



Case Report

Early atypical malignant transformation of diffuse low-grade astrocytoma: The importance of genotyping



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ABSTRACT

Diffuse astrocytoma (WHO grade II) has classically been considered a slow growing tumour, typically affecting young adults, with tendency for late malignant conversion. We describe a case of early atypical malignant transformation of diffuse astrocytoma seventeen months after complete surgical removal, as an intraventricular high-grade glioma (HGG). Retrospective laboratory findings for the presence of IDH 1/2 (isocitrate dehydrogenase) mutations were negative. There is growing evidence that IDH-wildtype (wt) astrocytomas behave more aggressively, therefore identifying IDH-mutation status should be mandatory in order to determine disease prognosis and guide treatment course.

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Transformación maligna atípica temprana de astrocitoma difuso de bajo grado: la importancia de genotipificar

RESUMEN

Clásicamente, el astrocitoma difuso (OMS II) se clasificaba como neoplasia de crecimiento lento, afectando a adultos jóvenes y con tendencia para conversión maligna tardía. Reportamos un caso de transformación maligna temprana de astrocitoma difuso de grado bajo 17 meses después de remoción tumoral completa, como glioma intraventricular de grado alto. Un análisis retrospectivo para la presencia de la mutación IDH 1/2 fue negativo. La

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t creciente evidencia demuestra que los astrocitomas IDH-wildtype se comportan de forma más agresiva, así que identificar la mutación IDH debería ser mandatorio para determinar el pronóstico y redireccionar el tratamiento de los astrocitomas.

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Introduction

The 2007 World Health Organization (WHO) classification of central nervous system tumours classified diffuse astrocytoma as a grade II diffusely infiltrating neoplasm characterized by a high degree of cellular differentiation and slow growth.¹ The 2016 update of the WHO classification² incorporates molecular parameters depending on IDH mutation status that have a growing role in the prognosis and treatment of these tumours and as such astrocytomas were further subdivided into 3 categories: diffuse astrocytoma (IDH mutant), diffuse astrocytoma (IDH-wildtype) and diffuse astrocytoma (NOS). In the pathogenesis of lower grade gliomas Lima et al.³ proposed a four-period development cascade made up of an occult stage, a silent stage, a symptomatic stage and a period of malignant transformation. IDH mutations take place early in the natural course of glioma development^{4,5} and occur in more than 70% of grade II astrocytomas.⁶ IDH-1/2 mutations have been associated with better prognosis⁴ while IDH-wt status has been linked with lower time to progression and shorter overall survival (OS).⁷ In this paper we present the case of a completely removed low-grade astrocytoma that recurred 17 months after surgery in a very aggressive pattern.

Case description

In January 2015 a 37-year-old male presented to the emergency department due to a partial seizure, with complete recovery. Neurological evaluation was normal. MRI showed a small left frontal lesion centred in the middle frontal gyrus, hypointense in T1 and hyperintense in T2 and FLAIR sequences, with no gadolinium enhancement and with no surrounding oedema, compatible with lower-grade glioma (LGG). He was submitted to a gross total resection of the tumour in April 2015 (see images in appendix). After surgery, he presented mild motor dysphasia that subsided in the following days. The histopathological diagnosis was that of a neoplasm with moderate cellular density consisting of astrocytic cells with discreet nuclear pleomorphism. No mitosis, necrosis or microvascular proliferation was found. Immunohistochemistry showed diffuse reactivity for glial fibrillary astrocytic protein (GFAP) and the Ki-67 index was 2%. The tumour was therefore classified as a diffuse astrocytoma (WHO grade II). Due to the understanding at the time of the absence of risk factors no complementary treatment was initiated and the patient was kept under clinical surveillance with serial MRI imaging. Seventeen months after surgery he developed rapidly progressive dysphasia, gait ataxia and mental confu-

sion. MRI showed a new non-enhancing deep frontal lesion contiguous with the surgical site and a contrast enhancing intraventricular mass compatible with tumour recurrence. The previous histopathological exam was reviewed and IDH-1/2 mutation and ATRX expression were looked for. ATRX expression was preserved with absence of IDH-1/2 mutant expression. Tumour recurrence as a higher-grade glioma was treated with radiotherapy and chemotherapy according to Stupp protocol but the patient passed away in May 2017.

Discussion

The presented case emphasizes the relevance of molecular profiling lower-grade gliomas. Prior to the 2016 WHO update on the classification of central nervous system tumours diagnosis, prognosis and neoplastic behaviour were based on histopathology and clinical criteria such as age and patient performance status and radiological features such as tumour volume/location and contrast enhancement characteristics. Grade II tumours with complete gross total resection could be followed with clinical and radiological surveillance, especially in younger adults with no neurological deficits before surgery, in tumours whose maximum diameter did not exceed 6 cm and with no contrast enhancement or midline shift.

Our patient presented with none of the factors previously associated with increased risk for malignant transformation. He had pre-surgical low tumour volume, a maximum tumour diameter of 3 cm and gross total removal had been achieved.

Indeed, by reviewing the literature the increasing evidence over the last two decades has shown that the extent of resection (EOR) is a major factor influencing patient OS in primary LGG.⁸ Early maximal surgical resection is also expected to delay malignant transformation.⁹ In fact, EOR and postsurgical residual volume still remain as independent prognostic factors significantly associated with longer survival, beyond tumour genomics.^{10,11}

In addition our patient had also presented with the following positive prognostic signs: age under 40, tumour presentation with epilepsy in the absence of focal neurological signs and a frontal or parietal tumour location.

As previously described, the histopathological examination did not show characteristics of malignancy.

Furthermore, at the time of the initial patient evaluation the diagnostic significance of the T2 - FLAIR mismatch sign reported by Patel et al.¹² and later confirmed by Broen et al.¹³ in identifying IDH mutant non 1p/19q codeleted astrocytomas had not been known.

Therefore the rationale behind the decision to maintain our patient in clinical and imagiological surveillance was based on the scientific knowledge at the time of tumour presentation, when tumor phenotype and histology were the main prognostic factors and IDH mutation was not routinely searched for.

Mondesir et al.¹⁴ describe the role of IDH 1/2 mutation in tumour oncogenesis while the Buckner study⁷ published in 2016 in the NEJM not only changed the treatment paradigm of lower-grade gliomas by showing the benefits in OS and progression free survival (PFS) of combined chemotherapy and radiotherapy versus radiotherapy alone but also highlighted the shorter survival time of astrocytoma patients with IDH-wildtype genotype.

In their review of the WHO 2016 classification of brain tumours Louis et al.² also report the more favourable outcomes associated with IDH-mutant astrocytomas and remark that IDH-wildtype LGG astrocytomas represent a rare diagnosis, probably sharing many genomic alterations with HGG such as glioblastoma.^{10,11}

Indeed, Hasselblatt et al.¹⁵ showed that the majority of diffuse IDH-wildtype astrocytomas share the molecular features of high-grade gliomas and follow a similar clinical course, possibly representing glioblastoma at an earlier stage.

In their systematic analysis of diffuse LGG Di Carlo et al.¹¹ also report the lower OS of IDH-wt astrocytomas but point out to the clinical heterogeneity and evolution of these tumours, therein further stratification depending on other concomitant genomic alterations should be a goal of future researches.

As such, our case translates the profound changes brought about by the increased understanding of how molecular genotyping has transformed the approach to the diagnosis, prognosis and treatment of brain tumours. Notwithstanding our patient having all the factors previously associated with good prognosis the absence of IDH 1/2 mutations was most likely the responsible factor behind such aggressive tumour behaviour and should have warranted a more intensive treatment.

Conclusions

The presented case highlights the importance of tumour genotyping. Our patient was treated based on imagiological and histological findings that pointed to a less aggressive type of tumour. As the 2016 WHO classification and other studies demonstrate^{2,15} tumour behaviour of lower-grade gliomas is more dependent on molecular than histological findings. This rearrange keeps together the tumours by clinical behaviour according to genetic profile instead of grouping them histopathologically but with different prognosis. Therefore, IDH mutation should be sought for in all astrocytomas and treatment should be directed accordingly.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neucir.2020.09.003>

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