



Case report

Multicentric oligodendroglioma: Case report and review of the literature

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ARTICLE INFO

Article history:

Received 16 December 2012

Received in revised form 26 February 2013

Accepted 28 February 2013

1. Introduction

A 38-year-old right-handed lady presented with a 1-month history of seizures. Her attacks began with a sudden wave of dizziness, followed by a feeling of unsteadiness as if she might fall; associated with sensory disturbance down the right side of her face, right arm and right leg. She denied any limb paralysis or shaking. The initial phase was followed by loss of recognition of her right arm and if standing she would fall.

She gave a history of epileptic seizures between the ages of six months to five years. She would wobble, appear strange and stare, be vacant and fall. She took Phenobarbitone during this period. She experienced two generalised tonic clonic seizures as a teenager. The first seizure occurred at the age of eleven and the second one at the age of fourteen and they were both precipitated by visual stimuli. The first attack happened when she was lying on the sofa with her head hanging over the back of it whilst watching TV upside down, the second one, she had just turned the TV on and was about a foot away when the bright display came on. She quickly turned away when she felt bright flashing lights across her right visual field, the same ones that had precipitated her seizure three years earlier. She also admitted to a feeling of flutters over her head during both events. She took sodium valproate until the age of twenty-three with no further seizures. No brain imaging or EEG was done after the childhood seizures.

Magnetic Resonance Image (MRI) (Fig. 1) revealed three separate lesions in the left frontal, left parietal and left occipital lobes. Along with MR spectroscopy a radiological diagnosis of low-grade multicentric glioma was made.

She underwent a left occipital mini-craniotomy and excision of occipital tumour and a left-frontal mini craniotomy and biopsy of the frontal space lesion. No intervention was carried out on the parietal lesion, given its close proximity to the sensorimotor cortex and normal MR spectroscopy. Post operatively there was no visual field deficit. She experienced attacks of flashing lights on her right visual field, with several episodes per month lasting minutes. She was treated with carbamazepine post-operatively. Seizures stopped eleven months after the operation and she remains seizure free, having withdrawn all antiepileptic medication for three years. Three-year follow-up MRI shows no new changes, annual follow up MRI continues.

We discuss the radiological, neuropathological and genetic findings encountered and review the literature.

2. Neuropathology

The specimen obtained from the occipital lesion (Fig. 2) revealed a large fragment of cerebral cortex with areas infiltrated by tumour cells consistent with a low-grade glioma with some features of an oligodendroglioma WHO grade II.¹ There was no evidence of necrosis; mitotic figures, blood vessel wall changes or ganglionic differentiation and the surrounding cerebral cortex did not contain evidence of cortical dysplasia or heterotopia. Immunohistochemistry with anti-Ki-67 (a marker of cell proliferation) showed a low proliferation index, anti-GFAP (Glial fibrillary acidic protein) demonstrated fibrillary processes. Tumour necrosis and vessel wall changes were absent. Similar histological and immunohistological changes were found in the frontal lobe specimen (Fig. 2). Both specimens were regarded as LGG WHO II with predominantly oligodendroglial features, but with an astrocytic component (GFAP positive staining). There was no evidence of ganglionic differentiation with anti-synaptophysin or neurofilament antibodies.

3. PCR analysis

DNA from occipital and frontal specimens showed loss of heterozygosity (LOH) in 1p/19q, and loss of 10q and 7p. Both the occipital and frontal sections showed mutations in the isocitrate dehydrogenase 1 (IDH1) gene and no mutation of the IDH2 gene. These findings are consistent with low-grade glioma.

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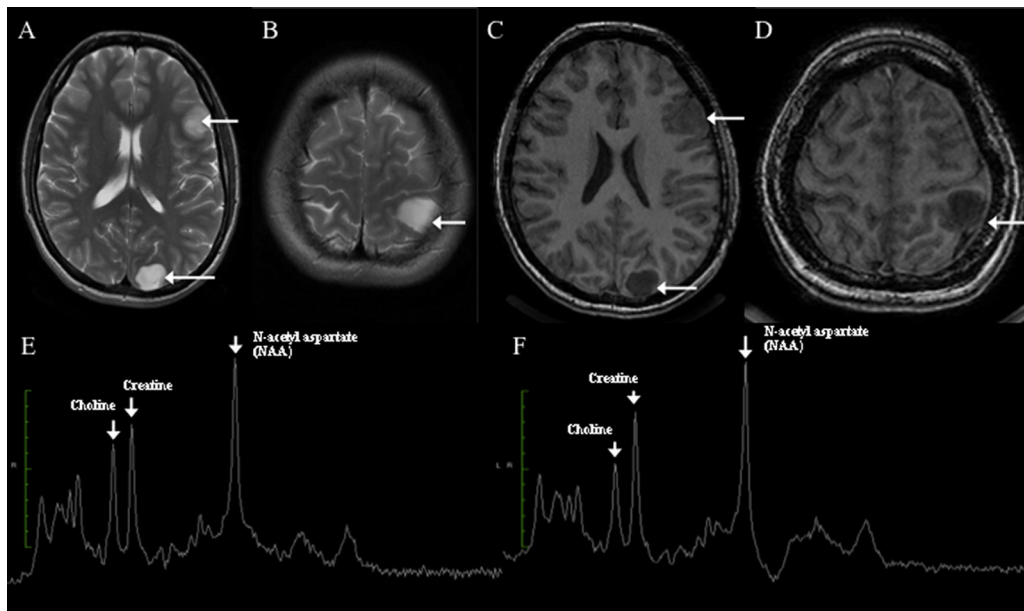


Fig. 1. MRI brain: (A) axial T2 showing occipital and frontal lesions, (B) axial T2 showing parietal lesion, (C) fast spoiled gradient echo (FSPGR) showing frontal and occipital lesions, (D) FSPGR showing parietal lesion. There was no enhancement to suggest high grade but there was some mass effect present at the time. MRI spectroscopy: (E) frontal lesion showed relative reduction in NAA compared to creatine and an increase in choline compared to creatine. NAA is a marker for normal neurones and axons, creatine is an internal standard and an increase in choline reflects an increase in cellular division. Spectroscopy of the occipital (F) was close to normal, supported by minimal reduction in NAA from the occipital lesion but no elevation in myo-inositol or choline. The parietal lesion had essentially normal spectroscopy.

4. Discussion

Low-grade gliomas are primary brain tumours that arise from glial cells. They are separated according to the glial type from which they arise, astrocytoma or oligodendroglioma. The World Health Organisation (WHO) classification divides astrocytoma into four grades (I–IV), from least to most malignant. Oligodendrogliomas are

classified, as grade II.¹ Low-grade gliomas are often mistakenly thought of as benign neoplasm and their association with neurological morbidity and mortality as well as their potential for anaplastic transformation disregarded.² Moreover, the optimum management of this type of tumour continues to be a matter of individual clinical judgement and subsequent debate due to the lack of sufficient data to inform the decision-making process.³

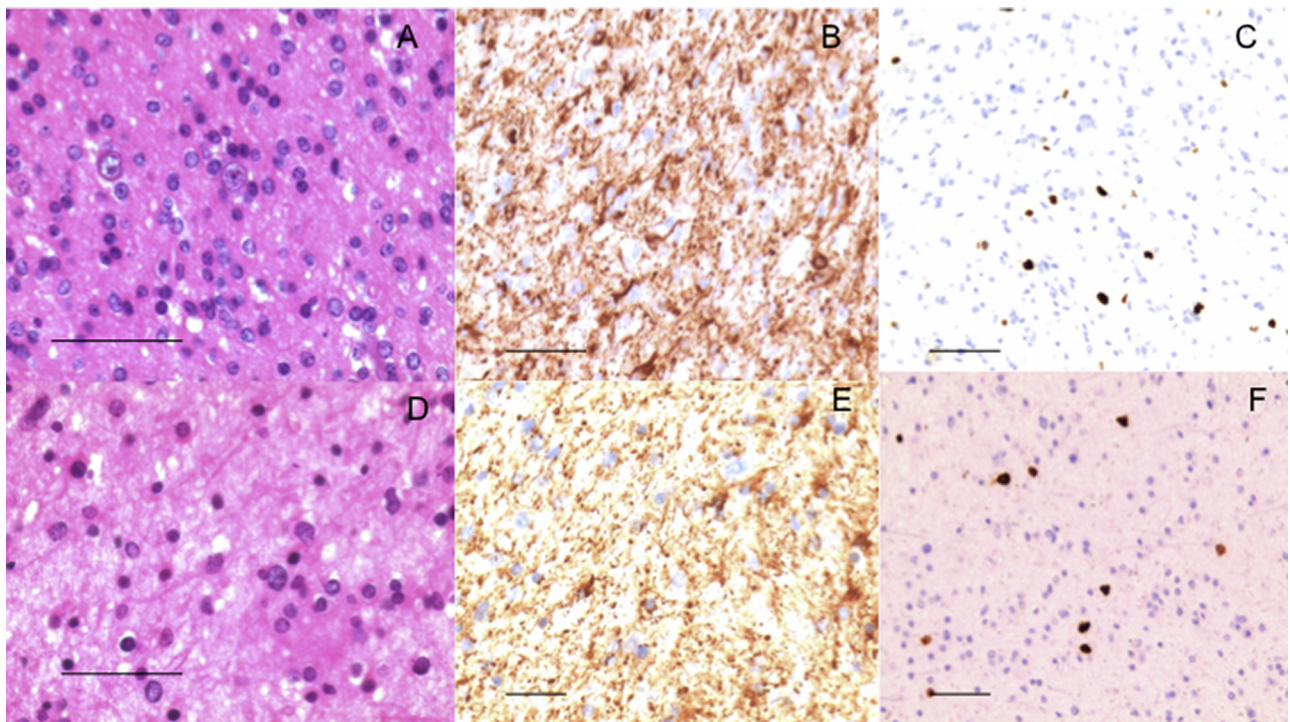


Fig. 2. Frontal (A)–(C) and occipital (D)–(F) tumour biopsies. A scale bar has been added 20 microns in length for each image. A/D Haematoxylin & Eosin stained paraffin wax sections showing detailed cellular morphology, similar morphology is seen in both. B shows anti-GFAP staining of fibrillary processes but not all nuclei are positively stained and E Anti-GFAP demonstrates fibrillary staining pattern. C/F Ki67 labelling demonstrating a low proliferation index similar in both tumours.

Although uncommon, the occurrence of multiple gliomas has been previously reported. They can be grouped in two main categories: multicentric and multifocal.⁴ The main difference is their mechanism of spread. Multifocal gliomas disseminate from a primary site⁵ along nerve fibre bundles, CSF channels and blood. Multicentric gliomas consist of separate entities, in different lobes or hemispheres, and show no spread or metastasis.⁶ The exact incidence of multiple gliomas is unknown, a range between 0.5% and 20% has been quoted in previous reports,⁶ with most reports describing two lesions in either separate or the same lobe. Whilst rare cases of oligodendrocytic gliomatosis cerebri have been reported in the literature,⁷ the lack of white matter involvement in imaging and pathology, stable neurological status and survival interval, make this alternative diagnosis unlikely. To the best of our knowledge, this is the first report of a case involving three separate low-grade supratentorial lesions in three separate lobes, two with the same histopathology and PCR analysis.

The morphological features in each tumour are of low grade gliomas LGG² (World Health Organisation II) of mainly oligodendroglial sub-type, but owing to the presence of positive anti-GFAP raises the possibility of a mixed tumour of oligodendroglial and astrocytic differentiation (Fig. 2). The loss of heterozygosity (LOH) 1p/19q supports the histological and immunohistochemical data; oligodendrogliomas are more frequently associated with LOH 1p/19q than the oligoastrocytomas.^{2,8,9} The LOH 10q/7p is unexpected but this test was repeated and considered robust.

IDH1 mutations occur mainly in low-grade gliomas (astrocytomas and oligodendrogliomas) and are retained during tumour progression.¹⁰ It also helps distinguish low-grade gliomas from other tumour entities where the mutation does not occur, or where it occurs very rarely.¹⁰ The presence of an IDH1 mutation also has an impact on prognosis, with median survival being 3.8 years for patients with mutated IDH1, as compared to 1.1 years for patients with wild-type IDH.¹⁰ Both the occipital and frontal sections showed mutation of the IDH1 gene in our patient, which would be consistent with her stable clinical status so far.

The previous history of occipital onset seizures with secondary generalisation as a teenager in our patient, suggests an occipital lesion may have been present from early teens, and the earlier childhood seizures may have also been lesional; this is not

possible to corroborate, as the patient did not have brain imaging at the time.

5. Conclusion

Multicentric low-grade oligodendrogliomas are uncommon and despite their initially insidious clinical presentation, they retain a potential for malignant transformation. Our case is unusual given the presence of three separate tumours. MRI and MRS, biopsy with histopathological and PCR analysis are needed for diagnosis. Optimal timing of surgery versus imaging surveillance only remains controversial, though with advances in imaging, neurosurgical techniques and other neuro-oncological treatments (radiotherapy and chemotherapy), and recognition that these tumours have the potential to transfer to high grade in time, supports an increasingly aggressive surgical approach.¹¹

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