

# **Midbrain Gliofibroma presenting in adulthood following ‘cure’ of a childhood intraventricular pilocytic astrocytoma**

Mohammad U Ahmad<sup>a b</sup>, Atik Baborie<sup>d</sup>, Barry Pizer<sup>g</sup>, David J Husband<sup>e</sup>, Conor Mallucci<sup>f</sup>, Michael D Jenkinson<sup>b c</sup>

<sup>a</sup>*School of Medicine and* <sup>b</sup>*Institute of Translational Medicine, University of Liverpool, Liverpool, UK.*

<sup>c</sup>*Department of Neurosurgery and* <sup>d</sup>*Neuropathology, The Walton Centre NHS Foundation Trust, Liverpool, UK.*

<sup>e</sup>*Department of Clinical Oncology, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK.*

<sup>f</sup>*Department of Paediatric Neurosurgery and* <sup>g</sup>*Paediatric Oncology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK.*

Corresponding author:

Mr Mohammad U Ahmad

School of Medicine

University of Liverpool

Cedar House, Ashton Street, Liverpool, L69 3GE, UK

Email: [m.u.ahmad@liverpool.ac.uk](mailto:m.u.ahmad@liverpool.ac.uk)

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## **Abstract**

**Introduction:** Gliofibromas are rare biphasic tumours with a good prognosis that usually occur in childhood. Rare adult spinal cases have been treated with radiotherapy. This report describes the case of a gliofibroma occurring in a young adult 10 years after a treatment for a childhood pilocytic astrocytoma.

**Case:** A 14 year old female underwent complete resection of a right lateral ventricle pilocytic astrocytoma confirmed on post-operative magnetic resonance imaging (MRI). At age 17, the tumour recurred and a second complete resection was performed. Due to the early recurrence she was placed on long-term MRI surveillance. At age 23, an enhancing left midbrain tumour was identified that was suspected to be a recurrent pilocytic astrocytoma. Following surgical resection the histopathology revealed a gliofibroma. Due to the growth of further tumour nodules she was treated with fractionated radiotherapy. There is no disease recurrence after 36 months follow-up and the patient remains well.

**Discussion:** Gliofibromas are tumours which usually occur in childhood, this case report identifies a rare occurrence in an adult. The childhood intraventricular pilocytic astrocytoma was in an anatomically distinct location to the midbrain gliofibroma. Radiotherapy can control these tumours and follow up is required to understand the long-term outcome and prognosis.

Key words:

Gliofibroma, pilocytic astrocytoma, surgery, radiotherapy

## **Introduction**

Gliofibroma is a rare biphasic tumour [1]. The majority occur as new tumours in childhood, with a favourable post-operative prognosis. Rarely these tumours occur in the spine in adults [2] and require treatment with radiotherapy. In this report we describe the case of a cranial gliofibroma in a young adult, that occurred 6 years after treatment of an intraventricular pilocytic astrocytoma.

## **Case Report**

A 14 year old female underwent gross total resection of a right lateral ventricle pilocytic astrocytoma that was confirmed on the post-operative magnetic resonance imaging (MRI) (figs. 1a-b). Routine surveillance MRI revealed tumour recurrence and she underwent further surgery at the age of 17 years. Complete resection was confirmed on the post-operative MRI and histopathology revealed a recurrent pilocytic astrocytoma. At age 23, a surveillance MRI revealed a small enhancing nodule in the left midbrain. The lesion was slightly hypointense on T1 (fig. 1c) and hyperintense on T2 weighted images (fig. 1d) with strong contrast enhancement (fig. 1e). Another pilocytic astrocytoma was suspected. In March 2011, a supracerebellar, infratentorial approach was performed. A greyish tumour with a good plane around the brainstem in the inferioromedial aspect was seen, with thick arachnoid superiorly and the tumour merging into fibrous looking tissue. A subtotal resection was performed and post operatively, she recovered well with no deficits. MRI confirmed a rim of enhancing residual tissue.

The histology (fig. 2a) showed strands of collagenous tissue with intervening thin trabeculae of GFAP and synaptophysin positive material. The overall appearance was reactive and did not

correlate with her previous pathology. In the absence of confirmed tumour she was placed on active MRI surveillance, but after 3 months the midbrain lesion progressed (fig. 1f) and in January 2012 she underwent a second resection. The histology (figs. 2c-f) showed a biphasic, moderately cellular neoplasm comprising both a glial (GFAP positive, fig. 2d) and a stromal component. The cells were fibrillary, occasionally epithelioid or clear shaped arranged in fascicles and nests within a dense reticulin positive stroma. Mitoses, necrosis and endothelial hyperplasia were absent. A few fat cells were present consistent with adipose metaplasia (figs. 2b,e,f). Immunohistochemistry showed that the cells were IDH1 negative. The proliferation rate was low (KI67 < 1%). The nuclei were INI1 positive. BRAF codon analysis was assessed as this is characteristic of some gliofibromas. However, repeated BRAF codon V600E analysis showed a low level of a mutation (the intraventricular biopsy was negative for this mutation). The following stains were negative: CD34, Desmin, NF160 and CAM5.2. The features were in favour of a gliofibroma. The histopathology of the childhood right lateral ventricle tumour (fig. 2a) showed typical features of a pilocytic astrocytoma (WHO grade I) with abundant Rosenthal fibres. In this specimen the tumour cells lacked the BRAF V600E mutation and the nuclei were INI1 positive.

At 8 months follow-up, the MRI showed interval progression of the small residual midbrain lesion with one new remote tumour nodule in the prepontine cisterns (figs. 1g-h). Further surgery was not feasible, and stereotactic radiosurgery was considered to have a high risk of radionecrosis, especially with respect to the midbrain lesion. The patient was treated with fractionated radiotherapy to a total dose of 54Gy in 30 fractions in January 2013. Intensity modulated radiotherapy (IMRT) using VMAT (Volumetric Modulated Arc Therapy, RapidArc™, Varian Medical

Systems, Palo Alto) was used to treat the five nodules present on the planning MRI, with minimisation of the dose to the intervening brain, with the maximum and mean dose to the hypothalamus and pituitary limited to 20.4Gy and 9.8Gy respectively. At last follow-up in October 2016 (42 months post-treatment) there was evidence of regression of two nodules, with no new tumour nodules. The patient was asymptomatic.

## **Discussion**

Gliofibroma was first described by Friede as a rare bimorphic tumour with a mixture of glial and fibroblastic origins [1]. The majority are supratentorial and occur in females during childhood. Our patient was under review following treatment of a childhood pilocytic astrocytoma, which tend to have a favourable 5 year survival rate of up to 97.3%. The pilocytic astrocytoma showed no evidence of local recurrence for 6 years, until a new distant midbrain lesion appeared. There was a distinct difference between the anatomical location of the pilocytic astrocytoma (right lateral ventricle) and the site of the gliofibroma within the midbrain.

The histogenesis of gliofibroma is not clearly understood and the possible hypotheses about its origin have not been confirmed [2]. Thus, gliofibroma may be regarded as a member of desmoplastic astrocytic tumours within a spectrum of malignant tumours such as gliosarcoma (WHO grade IV), or low-grade gliomas and glioneuronal neoplasms such as desmoplastic infantile ganglioglioma (WHO grade I) and non-glial tumours such as subtypes of meningiomas and solitary fibrous tumours. However, our case is distinct from these entities due to the lack of an anaplastic

malignant component or neuronal differentiation with the above immunohistochemical profile and failed detection of a BRAF V600E mutation. However, it should be noted that whilst BRAF mutation is considered a characteristic finding in gliofibroma, it is only present in around 50% of cases.

Therefore our patient has two pathologically different tumours in anatomically distinct locations, and importantly the patient had not received any prior cranial irradiation, nor were they syndromic. There was no family history of brain tumours or developmental abnormalities. Several gliofibroma cases have been reported [3], but none associated with previous childhood pilocytic astrocytoma. It is possible that this patient had two separate unrelated glial tumours, that arose sporadically or as a result of environmental factors. The absence of BRAF mutations in both tumours supports a non-genetic or familial cause, however whole genome sequencing would be required to confirm this.

The optimum management of gliofibroma is undefined. In most cases, the prognosis is favourable, with a clinical course without recurrence or metastasis. The majority of patients do not have aggressive growth or disease progression during follow up. The first line treatment for gliofibroma is gross total surgical resection. There have been four reported deaths due to gliofibroma in literature [1, 3, 4], however the follow up period is short; ranging from 2 months to 10 years. Radiotherapy has been used in four cases [1, 4, 5] and was ineffective at controlling the tumour with three patients dead within 18 months of treatment. However in our patient, fractionated radiotherapy has controlled the tumour for 3 years with no evidence of recurrence or progression.

Due to the rarity of this tumour, extended follow up is recommended in order to better understand the nature and long-term prognosis of these tumours.

## References

- [1] Friede RL. Gliofibroma. A peculiar neoplasia of Friede RL. Gliofibroma. A peculiar neoplasia of collagen forming glia-like cells. Journal of neuropathology and experimental neurology. 1978;37:300-13.
  
- [2] Prayson RA. Disseminated spinal cord astrocytoma with features of gliofibroma: a review of the literature. Clinical neuropathology. 2013;32:298-302.
  
- [3] Kim Y, Suh YL, Sung C, Hong SC. Gliofibroma: a case report and review of the literature. Journal of Korean medical science. 2003;18:625-9.
  
- [4] Vazquez M, Miller DC, Epstein F, Allen JC, Budzilovich GN. Glioneurofibroma: renaming the pediatric "gliofibroma": a neoplasm composed of Schwann cells and astrocytes. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc. 1991;4:519-23.
  
- [5] Sarkar R, Yong WH, Lazareff JA. A case report of intraventricular gliofibroma. Pediatric neurosurgery. 2009;45:210-3



## Figure legends

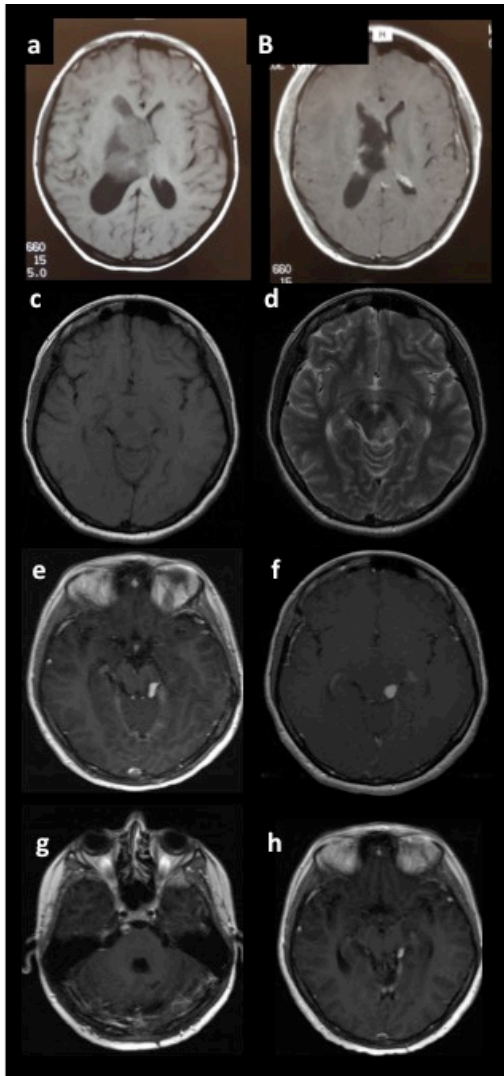


Figure 1

Axial MRI imaging showing the appearance of the original right lateral ventricle pilocytic astrocytoma (a) pre-operative T1-weighted and; (b) post-operative T1+gadolinium confirming complete surgical resection. The left-sided midbrain gliofibroma is shown on: (c) T1-weighted; (d) T2-weighted and; (e) T1+gadolinium sequences. At first recurrence the T1+gadolinium MRI revealed: (f) gliofibroma at the midbrain; (g) pre-pontine cistern and; (h) progression of left midbrain gliofibroma.

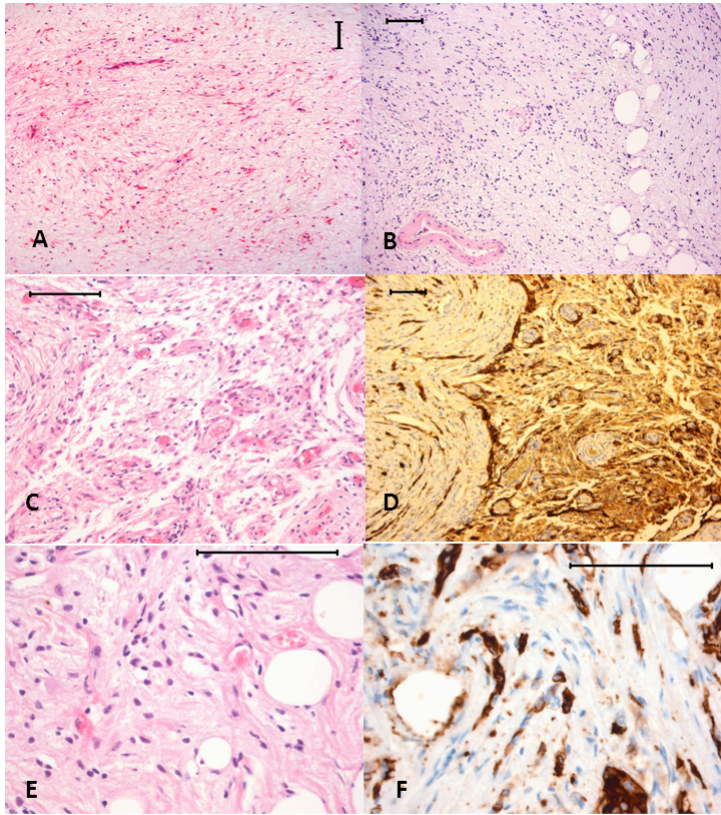


Figure 2

(a) Histopathological features of the pilocytic astrocytoma of the right lateral ventricle (H&E); (b) Histological features of the mid-brain biopsy specimens from the first surgery shows a biphasic tumour with a mainly glial component and intermixed fibrous tissue and focal mature fat cells (H&E ). (c) At second surgery the biopsy showed a biphasic neoplasm composed of a glial and a fibrous component (H&E); (d) GFAP positive component with islands of glial cells within the stromal component; (e) Higher resolution showing fibroglial cells admixed with mature fat cells (HE); (f) Isolated and clusters of glial cells expressing GFAP in the tumour.

Bar = 100 microns