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PII: S1878-8750(16)30679-9
DOI: 10.1016/j.wneu.2016.08.013
Reference: WNEU 4423

To appear in: World Neurosurgery

Received Date: 21 March 2016
Revised Date: 1 August 2016
Accepted Date: 3 August 2016


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\textbf{Key words:}

Adult
Low grade glioma
Metastasis
Pilocytic Astrocytoma

\textbf{Abbreviations list:}

CSF (Cerebrospinal Fluid)
CT (Computed Tomography)
JPA (Juvenile Pilocytic Astrocytoma)
LGG (Low Grade Gliomas)
MR (Magnetic Resonance)
MRI (Magnetic Resonance Imaging)
PA (Pilocytic Astrocytoma)
PMA (Pilomyxoid Astrocytoma)
WHO (World Health Organization)
Cranial pilocytic astrocytoma with spinal drop metastasis in an adult: case report and literature review

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Abstract

Background

Pilocytic astrocytoma (PA) is a benign neoplasm that typically occurs in the brain within the pediatric and adolescent age groups and is uncommon in adults. It rarely occurs within the ventricles and the overall prognosis is favourable. A pilocytic astrocytoma of the brain with spinal metastasis at presentation has never been reported in an adult.

Case Description

We report a case of a 47-year-old male presenting with sudden onset frontal headache associated with nausea and lethargy. This was on a background of a longer history of back pain and headache. Radiological imaging revealed an acute intraparenchymal hemorrhage in the right parietooccipital lobes with intraventricular extension within a peripherally enhancing heterogenous lesion. MRI spine revealed a sacral intradural tumor. The patient underwent surgical resection of the intracranial mass followed by debulking of the spinal lesion. Histopathological study revealed that both the cranial and spinal tumors were Pilocytic Astrocytoma.
Conclusion

This case illustrates a unique instance of hemorrhage into a cerebral pilocytic astrocytoma with a spinal metastasis. To our knowledge, this is the first such case reported in an adult. We review the literature on the subject.

Introduction

Juvenile pilocytic astrocytoma (JPA) is a WHO grade I brain tumor which occurs commonly in children and has an excellent prognosis. The annual incidence in adults is approximately 4.8 per million people\(^1\) and the reported incidence after age 45 is less than 0.1 cases per 100,000.\(^2\) The unpredictable and variable growth patterns of pilocytic astrocytoma in the pediatric population have been frequently described in the literature, since early reports by McLaughlin et al in 1976.\(^3\)

Although PA is classified as a World Health Organization (WHO) grade 1 tumor\(^4\), the literature indicates that PAs can be multicentric, disseminate into the leptomeninges and rarely undergo malignant transformation.\(^5,6,7,8\) Intraventricular PA have been infrequently reported in the literature. Intraventricular tumors constitute <1% of all brain tumors and 10% of these are found to be PA.\(^9\) Direct cellular extension of tumour into subarachnoid space or hematogenous dissemination may result in leptomeningeal spread and distal central nervous system metastases may occur from CSF seeding.\(^10\) The mechanism and biology of metastatic pilocytic astrocytomas is poorly understood.
PA appears to have distinct pathophysiological and clinical presentations in adult compared with pediatric populations. Pediatric PA typically arise in the cerebellum, brainstem and the hypothalamus, whereas adult PA is more likely to occur in the cerebral hemispheres.\textsuperscript{11} It has been postulated that supratentorial PA have distinct biological behaviour when contrasted with infratentorial PA.\textsuperscript{1} Hasselblatt et al found that BRAF-KIAA1549 fusion mutation was significantly lower in the adult PA, particularly those with a supratentorial origin.\textsuperscript{12} Bandopadhayay et al concluded from a long term outcome series of 4040 children with low grade gliomas (LGG) that the natural history of pediatric LGG is distinct from their adult counterparts. LGG diagnosed before age 22, has a lower risk of malignant transformation.\textsuperscript{13} PA is associated with higher mortality in adult patients when compared to children\textsuperscript{10} and have higher procedural morbidity rates following surgical resection due to factors such as location of tumor, extent of tumor resection and age.\textsuperscript{14,15}

The incidence of leptomeningeal spread reported in the literature varies from 3.7\% to 12\%,\textsuperscript{4} and has not been shown to indicate worse prognosis. Mamelak defined multicentric tumor as either diffuse subependymal or leptomeningeal dissemination beyond the margins of the primary tumor or as discrete nodular disease separate from the primary tumor mass.\textsuperscript{16} Diffuse leptomeningeal dissemination has been reported in both children and adults.\textsuperscript{17,18,19,20,21} We present the first adult patient to be diagnosed with more than one Pilocytic Astrocytoma tumor at presentation and with a hemorrhage into the intracranial tumor. The case is discussed and the relevant literature is reviewed.
Case report

A 47-year-old male presented with sudden onset severe frontal headache with retroorbital pain, nausea and lethargy. The patient had a past history of chronic back pain and occasional headaches, but was otherwise well, with no significant past history. The patient was in full-time employment. On examination the patient was alert and oriented and had no neurological deficits. He was hemodynamically stable. Initial CT brain revealed an acute right parietooccipital intraparenchymal hemorrhage surrounded by edema causing 5mm of midline shift to the left and early hydrocephalus. The post-contrast CT and MRI sequences revealed heterogeneous enhancement of both the intraparenchymal and intraventricular components of the hemorrhagic mass. There was surrounding oedema (Figure 1). Neuroaxis MR imaging revealed a gadolinium-enhancing spherical mass, 2.5 cm in diameter within the thecal sac immediately posterior to the S1-S2 disc space (Figure 2a). This lesion was thought likely to represent a metastasis. There was no evidence of spread to the cervical or thoracic region. The patient had no, sensory changes, or bowel or bladder dysfunction. The patient underwent a right stereotactic temporal craniotomy and resection of tumor. Intraoperatively the lesion was vascular and enmeshed within the choroid plexus. The patient tolerated the procedure well and intriguingly the patient’s long standing back pain resolved following the craniotomy. Immediate post-operative MRI brain revealed a small residual component behind the choroid in the occipital horn of the right lateral ventricle (Figure 3a).

Histopathological analysis showed fragments composed of GFAP immunoreactive astrocytic cells (Figure 4a), that in some areas showed a piloid bi-polar appearance
and in other areas a looser pattern of astrocytes with a background of hyalinised vessels and hemosiderin macrophages (Figure 4b). The neoplastic cells showed uniform nuclei with occasional degenerate nuclear atypia and the cytoplasm was demonstrably piloid consistent with pilocytic astrocytoma. There were no pseudovascular or true rosettes. No necrosis or microvascular endothelial hyperplasia was noted. The Ki67 index was less than 2% (Figure 4c). The tumour was IDH1 mutant (IDH1 R132H) negative. Fluorescence in situ hybridization (FISH) testing for BRAF:KIAA fusion proteins was not performed.

The patient underwent laminectomy and resection of the sacral tumour, 1 month later. Intraoperatively, an encapsulated soft tumor was found entangled by nerve rootlets, some of which were adherent to the capsule as was the filum terminale. An arachnoid plane was developed and the tumor removed, leaving minimal residual capsule adherent to the nerve rootles. The patient had no postoperative complications.

Histopathology of the sacral tumor revealed features similar in morphology to the original intraventricular tumor with a lesser component of hyalinised vessels (Figure 4d). The astrocytic cells were rounded in outline and bland and there were moderate numbers of the astrocytic cells with circumferential nuclear location. There was a fine cobweb matrix of fibrillary processes and granular bodies were observed. Hemosiderin macrophages were present. No mitotic figures seen. A diagnosis of pilocytic astrocytoma was made.
The consensus at the neuro-oncology multidisciplinary meeting was to observe the residual intracranial lesion. An MRI at 1 month showed no change. However, at 6 months the patient developed recurrence of back pain and mild headache. MRI revealed enlargement of the intraventricular lesion (Figure 3c). The spine lesion showed no evidence of residual or recurrent tumor (Figure 2b). The patient underwent a repeat resection of the intraventricular lesion. A gross macroscopic resection was achieved. Post-operative MRI confirmed no residual tumour (Figure 3d). The patient has remained well and at latest follow-up at 24 months there is no evidence of recurrent disease in the brain or spine.

**Discussion**

Pilocytic astrocytoma is a histologically benign tumour that has an excellent survival rate, typically occurring in the paediatric population. However, it can uncommonly manifest with leptomeningeal spread and there are currently 30 such paediatric reports describing metastatic pilocytic astrocytoma. Risk factors for dissemination include a hypothalamic location of the primary tumour, partial resection, and age less than 3 years at initial diagnosis. The mechanisms and predictive prognostic factors are not well understood. Of the various spread patterns summarised by Figueiredo et al in 2003, leptomeningeal spread after subtotal resection appears to be more common than development of a solitary distant metastasis. We report the first case of simultaneous cranial and spinal pilocytic astrocytoma in an adult.
A plausible explanation for the mechanism of spread of PA is via subarachnoid flow of cerebrospinal fluid to the spine as well as low flow regions like the sylvian fissures, basal cisterns and cauda equina. Obana et al reported a case of a 10-year-old boy who presented initially with a hypothalamic region JPA which metastasised to the left cerebellar tonsil and the lumbosacral region eight years later. The histopathology showed no evidence of malignant transformation. Versari et al reported the case of a 7 year-old boy with a chiasmatic JPA who presented three years later with a lumbar intradural extra-axial metastasis. However, the reverse spread pattern of an intraspinal PA presenting with disease intracranially have also been reported.

Faria et al reported a metastasis in the contralateral parenchyma and hypothesized that the spread was through white matter tracts, a pathway not previously reported in pilocytic astrocytoma. Overall the pattern of disease spread has not been shown to reflect aggressive tumour biology or malignant transformation.

Pilocytic astrocytoma is uncommonly seen in the adult population and only 17% of all PA present after age 30. A review of the literature reveals four cases of adult metastatic PA. Crabtree et al reported a 26 year-old male who presented with a spinal PA after previous surgery 18 years earlier for resection of a cranial PA in childhood. Jusue-Torres et al described the case of a cervical PA first presenting in adulthood, which was locally recurrent and eventually metastasised to the brain. Claus et al also described an adult case of spinal PA who later presented with obstructive hydrocephalus secondary to an intraventricular tumour, however the pathology of the metastasis revealed Glioblastoma Multiforme. Bohner et al described the only case of a pilocytic astrocytoma presenting as primary diffuse leptomeningeal gliomatosis in a 25 year old female patient. Figueiredo et al commented on the role of antigenic factors and metabolic capacities in determining
the spread of the disease.\textsuperscript{19} The pattern of spread for any given case of pilocytic astrocytoma and the length of time to recurrence, metastasis or malignant transformation remains unknown and when possible warrants reassessment of initial tumour specimen.

The simultaneous presentation of multiple tumours in our case raises the possibility of multifocal genesis of pilocytic astrocytoma. There are no histochemical markers or molecular diagnostic techniques to confirm this hypothesis. Alternatively, it can be speculated based on the periventricular location of the tumor nodule, which infiltrates the ventricle that the primary cranial tumour has over time spread via CSF seeding to the sacral region and is therefore a drop metastasis. It is most likely that this is a type of leptomeningeal dissemination and the patient has remained largely asymptomatic up till the onset of acute headache explained by the intratumoral hemorrhage.

Hemorrhage into a PA is uncommon. White et al reported 11 cases of hemorrhagic pilocytic astrocytoma from 1994 to 2005 out of a total of 138 (8%), a higher incidence than previously reported.\textsuperscript{29} Abnormal vasculature and the presence of microcalcifications within hemorrhagic PAs have been identified as distinguishing histologic features, but are not always seen.\textsuperscript{30} Shibao et al found that patients with hemorrhagic PAs seem to be distributed in the older age population and reportedly abundant abnormal vessels were found in some adult patients but rarely in patients less than 20 years old.\textsuperscript{31} Although our case is that of an adult PA, it is the first one reporting a metastatic PA presenting with an intrallesional hemorrhage.
The histopathology of our case was specifically analysed for differential diagnoses of other low grade gliomas. Pilomyxoid astrocytoma has higher rates of metastasis when occurring in the intraventricular location as compared with pilocytic astrocytoma. Tsugu et al reported 5 pediatric cases of pilomyxoid astrocytoma (PMA) with characteristic histopathology findings including a monomorphous pattern with a myxoid background; an absence of Rosenthal fibers and eosinophilic granular bodies; and more aggressive clinical behaviour. Interestingly, PMA were previously considered a subtype of PA and then became a separate entity, until only recently. They are grouped together in the 2016 WHO guidelines as astrocytomas that have a more circumscribed growth pattern, lack IDH gene family alterations and frequently have BRAF alterations. The case we present does not show characteristic PMA subtype findings and no aggressive features were identified in the cranial or spinal specimens.

The molecular biology of pilocytic astrocytomas is not well understood. Forsyth et al evaluated supratentorial pilocytic astrocytomas and found no histologic grade or flow cytometric characteristics to be associated with worse prognosis. The biomarker of Ki67 is characteristically less than 5% in low grade gliomas but Paixao et al reported higher medium values (>10%) in their cases of recurrent and more aggressive pilocytic astrocytomas. Szymbas et al used comparative genetic hybridization on 18 surgical specimens, which had been verified with immunohistochemical stains and microscopy, and found DNA imbalances on chromosome 19 to classify PA into two subtypes. Chromosome 19 has been strongly linked to astrocytoma tumorigenesis. The gene fusion product BRAF-KIAA1549, which is present in 50-100% of the patients with PA, considerably higher than in other low-grade tumours, is considered
highly specific for PA\textsuperscript{38} and is predictive of a better clinical outcome in subtotally resected low grade gliomas.\textsuperscript{39} Specific genes have been implicated in more aggressive forms of low grade gliomas such as germline mutations of NF1 gene.\textsuperscript{40} Mistry et al have recently reported on the frequency of BRAF V600E mutation, which is significantly higher in pediatric low grade gliomas that transformed to high grade gliomas compared to ones that did not transform.\textsuperscript{38} The 2016 WHO Classification of Tumors of the central nervous system states the importance of testing for genetic biomolecular markers especially when there are discordant histology results: “the genotype trumps the histological phenotype”.\textsuperscript{4}

Pilocytic astrocytoma is associated with higher mortality in adult patients than in children, and survival is inversely related with age in adults.\textsuperscript{10} Poor prognosis has been reported for adult patients with leptomeningeal dissemination.\textsuperscript{3,25} Age at diagnosis, histology, primary site, radiation, and degree of initial resection are all important prognostic factors.\textsuperscript{12} Gross total resection of low grade gliomas can be curative however the location of the tumour within eloquent areas of the brain may prevent complete excision. Radiotherapy following subtotal resection of PA has been associated with anaplastic transformation in 1.8% cases\textsuperscript{15} and the administration of radiation was associated with worse outcome in a large study of 4040 pediatric low grade glioma patients.\textsuperscript{12} Additionally van den Bent et al showed that early radiotherapy after surgery lengthens the period without progression but does not affect overall survival and concluded that radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored.\textsuperscript{41} For the case presented, early radiotherapy was not given and instead the patient was monitored radiologically at regular intervals.
Conclusion

Our case is unique, as to our knowledge it is the first reported adult case of multiple discrete PAs at presentation and the first to present with an acute hemorrhage. There are four other reported cases of adult PAs that have metastasised. However in some of these cases, the subsequent pathology potentially questions the initial diagnosis. Our case demonstrated a benign histopathological profile which is typical for PA in both lesions. Although this report is limited by relatively short follow up, at 24 months the patient has remained well with no evidence of recurrent disease.
References


Figure 1. a) Preoperative MRI (T1 Axial with gadolinium) showing right sided enhancing intraventricular lesion with surrounding edema. b) MRI (Flair Axial) showing surrounding Vasogenic edema
Figure 2. a) Preoperative Lumbar Spine MRI (Sagittal T1 with gadolinium) showing intradural lesion at S2 level b) Post operative 16 month follow up MRI (Sagittal T1 with gadolinium) showing no residual or recurrent tumour.
Figure 3. a and b) Postoperative MRI (T1 Axial T1 with and without gadolinium respectively) showing residual intraventricular lesion. c) Postoperative 6 month follow up (T1 Axial with gadolinium) showing enlargement of residual tumour d) 24 month follow up (T1 Axial with gadolinium) showing no evidence of residual or recurrent lesion.
Figure 4. a) [H&E, x200 magnification] GFAP immunoreaction shows strong GFAP reactivity of astrocytic cells, highlighting the piloid appearance b) [H&E, x200 magnification] Cranial tumor specimen showing piloid astrocytic cells (arrow head), granular bodies (long arrow) and other looser areas with bland rounded nuclei and scattered cells with peripheral nuclei. A background of hyalinised vessels and haemosiderin macrophages c) [H&E, x200 magnification] Ki67 immunoreaction highlighting lack of evident reaction within any cells in this field x 200 magnification d) [H&E, x200 magnification] Sacral tumor with similar characteristics to cranial tumor.
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Highlights

- We present an adult case of simultaneous cranial and spinal pilocytic astrocytomas
- A unique instance of hemorrhage into a cerebral pilocytic astrocytoma with a metastasis
- Gross total resection of low grade gliomas can be curative however the location of the tumour within eloquent areas of the brain may prevent complete excision
- Pilocytic astrocytoma is associated with higher mortality in adult patients than in children
- Close monitoring of residual pilocytic astrocytoma is recommended