Long-term outcomes of primarily metastatic juvenile pilocytic astrocytoma in children

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OBJECTIVE Primarily metastatic juvenile pilocytic astrocytoma (JPA) is rare, likely representing 2%–3% of all cases of JPA. Due to the rarity of primarily metastatic JPA, there is currently no standard treatment paradigm and the long-term outcomes are not fully known. The goal of this case series was to add to the current understanding of this disease process.

METHODS The authors searched a comprehensive database of pediatric patients with brain and spinal cord tumors treated at Lucile Packard Children's Hospital from 1997 to 2016 and identified 5 patients with primarily metastatic JPA. A retrospective chart review was performed and details of the patients' treatment and clinical course were recorded for further analysis.

RESULTS For the 5 patients with primarily metastatic JPA, the mean follow-up period was 12.3 years. All patients in our series had biopsies or subtotal resections and upfront treatment. Three patients were treated with chemotherapy alone, one was treated with chemotherapy and radiotherapy, and one was treated with radiotherapy alone. Four patients had stable disease after initial treatment, and one patient had multiple episodes of progressive disease but underwent successful salvage therapy and has had stable disease for 19 years. One patient died of an intracerebral hemorrhage 10 years following initial radiation treatment believed to be secondary to radiation vasculopathy.

CONCLUSIONS Evaluation of the entire neuraxis should be performed in all instances of initial JPA diagnosis to properly assess for primarily metastatic disease. Many patients with primarily metastatic JPA will have stable disease after upfront treatment, although the higher rate of stable disease found in this series relative to other reports is likely secondary to the small sample size.

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KEY WORDS metastatic; juvenile pilocytic astrocytoma; long-term outcomes; oncology

JUVENILE pilocytic astrocytoma (JPA) is the most common brain tumor of childhood.¹¹ It is typically indolent and localized in its growth and responds well to treatment with excision or local radiation treatment, brachytherapy, and/or chemotherapy for inoperable lesions.^{3,4,7,9,14} Accordingly, long-term survival and progression-free survival (PFS) rates in patients with JPA are high.^{1,7,11}

A small subset of patients with JPA present with metastatic disease on initial evaluation, a disease process we will refer to as “primarily metastatic” JPA. The true incidence of metastatic disease at presentation is unknown, as historically not all patients have undergone imaging of the entire neuraxis at diagnosis. The most robust account of the incidence of clinically diagnosed metastatic low-

grade glioma (LGG) comes from the German HIT-1996 study in which 2.8% of 1181 children with LGG presented with metastatic disease.⁷ This is in line with other studies, which have estimated that 2%–5% of children with LGGs present with metastatic disease.^{2,8,10,13} Due to the rarity of primarily metastatic JPA, patterns of presentation, optimal treatment paradigm, responsiveness to treatment, and long-term outcomes remain unclear. Additionally, most series regarding metastatic pediatric LGG do not separate JPA from other pediatric LGGs.

In this study, we present a single-institution series of pediatric patients who had primarily metastatic JPA seen at the time of initial diagnosis and a mean follow-up of greater than 10 years.

ABBREVIATIONS JPA = juvenile pilocytic astrocytoma; LGG = low-grade glioma; PFS = progression-free survival.

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Methods

We searched a comprehensive database of pediatric patients with brain and spinal cord tumors treated at Lucile Packard Children's Hospital from 1997 to 2016 and identified 5 patients with primarily metastatic JPA. Imaging of the entire neuraxis became part of the standard imaging protocol for all new patients with brain tumors in 2000. Details of the patients' treatment and clinical course were recorded for further analysis. Data on patient treatment, demographics, and outcomes were collected under IRB-approved protocol and accessed initially using the clinical electronic medical record and then anonymized. All available imaging studies were reviewed, and the pathological diagnosis was confirmed based on documentation within the electronic medical record.

Results

Five patients with metastatic JPA were identified in our

database and data were reviewed retrospectively. All patients had imaging studies of the neuraxis taken at presentation. Two patients had intracranial metastatic disease identified on index cranial imaging, 2 patients presented with symptomatic spinal lesions in addition to intracranial lesion(s) at presentation, and 1 patient had asymptomatic spinal lesions identified by protocol imaging of the entire neuraxis. All patients underwent subtotal resection or biopsy. Age at diagnosis ranged from 2 to 16 years (mean age 8.3 years). Four patients were male and one was female. None of the patients had neurofibromatosis or stigmata of neurofibromatosis. All patients had midline supratentorial tumors in addition to those at other sites. The mean duration of follow-up as well as overall survival was 12.3 years (range 2.5–26 years). All patients received upfront treatment: 3 with chemotherapy, 1 with chemotherapy and craniospinal irradiation, and 1 with craniospinal irradiation only. Detailed treatment regimens are outlined in Table 1. Four patients had stable disease after undergo-

TABLE 1. Treatment regimens for 5 patients with primarily metastatic JPA

Case No.	Sex	Age at Dx (yrs)	Tumor Location & Initial Surgical Treatment	CSF Diversion	Initial Treatment	Salvage Treatment	FU (yrs)	PFS (yrs)	Death	Complications/Sequelae
1	F	2	Hypothalamus (biopsied), cerebellum, spine	No	Procarbazine, CCNU, vincristine, dibromodulcitol, & 6-thioguanine	Carboplatin/vincristine; 1 yr later w/ further progression treated w/ CSI; 4 yrs later w/ new spinal & cerebellar lesions treated w/ oral etoposide; 2 yrs later progression of cerebellar lesion treated w/ SRS to that lesion; subsequent 19 yrs w/ stable disease	26	2	No	Hypothyroidism, visual impairment
2	M	3.5	Hypothalamus (STR), spine	VPS	STR of hypothalamic lesion; 4 cycles carboplatin/vincristine & CSI	Not applicable	20	20	No	Endocrinopathies including precocious puberty & hypopituitarism, asymptomatic cerebral infarct
3	M	11.5	Suprasellar mass, diffuse spinal disease (resection of symptomatic spinal tumor)	VPS	CSI	Not applicable	10	10	Yes	Paraplegia from initial spinal disease; recurrence of spinal cyst ultimately requiring marsupialization; death from ICH likely secondary to radiation treatment
4	M	8.5	Suprasellar/hypothalamic mass w/ lt frontal subependymal met (met was resected)	No	8 cycles carboplatin/vincristine	Not applicable	3	3	No	Precocious puberty at diagnosis but no further sequelae
5	M	16	Tectum/hypothalamus, T2–3, T9–10, & L4–5 lesions (biopsied)	ETV	8 cycles carboplatin/vincristine	Not applicable	2.5	2.5	No	None

CSI = craniospinal irradiation; Dx = diagnosis; ETV = endoscopic third ventriculostomy; FU = follow-up; ICH = intracerebral hemorrhage; met = metastasis; SRS = stereotactic radiosurgery; STR = subtotal resection; VPS = ventriculoperitoneal shunt.

ing the initial treatment paradigm. One patient had multiple episodes of progressive disease but has had stable disease for 19 years following additional chemotherapy, craniospinal irradiation, and stereotactic radiosurgery to treat to a recurrent lesion. No patients died of progressive disease. One patient died 10 years after initial diagnosis and treatment of a massive intracerebral hemorrhage. No recurrent or progressive intracranial disease was noted during his most recent follow-up examination prior to his fatal hemorrhage, and the hemorrhage is presumed to have been associated with his radiation treatment. Three patients required CSF diversion (2 with a shunt and 1 with endoscopic third ventriculostomy).

Illustrative Case

The 16-year-old boy in Case 5, who was previously healthy, presented with a 1-month history of headache and blurred and darkened vision; he was found to have mydriasis and papilledema on ophthalmological evaluation. Brain and spine MRI showed a midline diencephalic lesion causing obstruction of the cerebral aqueduct and obstructive hydrocephalus; a right internal auditory canal lesion; and T9–10, T2–3, and L4–5 lesions (Fig. 1). An endoscopic third ventriculostomy was performed. Five days later an open biopsy of the L4–5 lesion was performed. The pathological diagnosis was pilocytic astrocytoma. Following discussion among members of a multidisciplinary tumor board, a treatment course of 10 cycles of carboplatin and vincristine as per Children's Oncology Group protocol ACNS-A9952 was recommended. Eight courses of treatment were completed before the patient and his family requested cessation. The patient underwent neuraxis MRI every 3 months for 2 years and currently undergoes MRI monitoring every 6 months. During and after treatment he has had imaging-confirmed stable disease. At his most recent follow-up, the patient is 35 months postdiagnosis and 23 months posttreatment, is doing well with no symptoms, and is currently enrolled as a freshman at college.

Discussion

Primarily metastatic JPA is a rare disease for which the expected outcome and ideal treatment paradigm remain unclear. Midline supratentorial JPA represents a significant majority of the reported cases of metastatic JPA in the literature, which is corroborated by our data showing that all 5 patients had midline supratentorial JPAs in addition to lesions at other sites. The recent publication of the data from the German HIT-1996 trial as well as a large series from St. Jude Children's Research Hospital have significantly increased breadth of the reported experience involving patients with metastatic LGG.^{2,7} These studies included patients with primarily and secondarily metastatic LGG, and the studies were not specific to primarily metastatic JPA. Thus, while the majority of patients in both studies did have JPA (17 of 22 patients with primarily metastatic LGG had JPA in the HIT study, and 23 of 38 patients in the St. Jude cohort had JPA), the ability to make accurate comparisons with our cohort is limited. The St. Jude series in particular has excellent long-term follow-up

FIG. 1. Case 5. Imaging studies of the patient at diagnosis. **A:** Sagittal T2-weighted MR image of head. **B–D:** Sagittal T1-weighted postcontrast MR images of the cervical, thoracic, and lumbosacral spine.

and reports a poor long-term outcome in patients with metastatic LGG as 50% survival at 15 years after diagnosis, with 93% of deaths due to progressive disease. In the HIT study, among the 23 patients with sufficient follow-up, the 10-year overall survival in those with primarily metastatic LGG was 73%. Progression-free survival in both series was low, with the St. Jude group reporting a 5-year PFS of 8.1% and the HIT study reporting a 5-year PFS of 6% with a median time to progression of 16 months. Additionally, in another series, Hukin et al. reported a 5-year PFS rate of 17%.⁸ In contrast, in our series 2 of 3 patients had PFS at 5 years and no patient died of progressive disease.

This discrepancy in outcome may be a result of the smaller numbers of our study, differences in the biology of primarily metastatic compared with secondarily metastatic disease, or possibly that JPA may be more responsive to treatment or less aggressive than the broader category of pediatric LGGs that were included in the larger series. Of the 3 patients with greater than 10 years of follow-up in our series, none died of progressive disease and, to our knowledge, our 2 patients with 20 and 26 years of follow-up represent the longest reported survival for patients with primarily metastatic JPA. The rate of CSF diversion in our study was 60%, which is in line with the HIT study, in which 57% of patients underwent shunt surgery.

The preponderance of hypothalamic JPA in patients with metastatic JPA, both in our series and others, suggests a higher propensity for metastatic dissemination in hypothalamic JPAs than those in other locations. It is not possible to definitively ascertain the original location of the tumor in patients who present with metastatic disease.

FIG. 2. Recommendations for the diagnosis and treatment of metastatic JPA. ETV = endoscopic third ventriculostomy; VPS = ventriculoperitoneal shunt; XRT = radiation therapy. Figure is available in color online only.

However, the preponderance of hypothalamic primary tumors in the cohort of patients who developed delayed metastatic disease in both the HIT and St. Jude trials is consistent with the hypothesis that the primary site for these tumors is in the hypothalamus.

The optimal treatment regimen for primarily metastatic JPA is unclear. The treatment of patients in our series was varied and unfortunately does little to add additional perspective due to the lack of a consistent protocol for treatment. The one death in our series highlights the potential risks of radiation therapy in the pediatric population. However, the 2 patients in our series with greater than 20 years of follow-up and long-term stable disease both received radiotherapy and chemotherapy. The 2 more recently treated patients in our series received upfront carboplatin/vincristine, which is in line with current trends in the treatment of nonresectable JPA.^{2,4,12,16} In the HIT study, 3 of 4 patients treated with upfront radiation alone had progression within 1 year, and only 6% of patients treated with upfront carboplatin/vincristine had PFS at 5 years.⁷

It also remains unknown if upfront treatment alters the natural history of the disease in the absence of clear signs of radiographic progression. The patients in this series who were treated with upfront chemotherapy had no radiographic response to treatment other than stable disease, raising the question as to whether treatment alters the biology of the tumor toward a more dormant or quiescent phenotype or, alternatively, is not disease modifying. The best

evidence for treatment again comes from the HIT study. Notably, in the HIT study, 8 of 9 children with metastatic LGG who were observed without treatment had progressive disease, with 4 dying from disease progression. In contrast, of the 24 children treated with upfront carboplatin/vincristine, 25% of children showed some degree of radiographic response to chemotherapy and 76% had stable disease.¹⁶ The stable disease seen in the children in our series is consistent with the high rates of stable disease seen in the patients treated with chemotherapy in the HIT study. The indolent nature of these metastatic lesions posttreatment warrants further investigation, as it is a rare phenomenon among metastatic tumors across histological types.

As our understanding of the molecular biology of JPA and metastatic JPA evolves, molecularly targeted therapies may play a larger role in the treatment of metastatic JPA. Altered BRAF function plays a prominent role in the pathology of LGG with 5%–15% of JPAs harboring BRAF V600E mutations and up to 65% of posterior fossa JPAs harboring a *BRAF*–*KIAA1549* fusion.⁵ Similar results have been found in disseminated LGG.⁶ In our series, the one patient who had testing for the V600E mutation was negative. The BRAF V600E mutation is targetable with vemurafenib, which has been successfully used in pilomyxoid astrocytoma, suggesting that targeting of the downstream MAPK pathway may be a viable option going forward.¹⁵

Based on the accumulated literature and our institutional experience, albeit small due to the rarity of this condition, we recommend the following for the diagnosis and treatment of metastatic JPA outlined in Fig. 2. All children with newly diagnosed CNS tumors should undergo MRI of the entire neuraxis to aid in the timely diagnosis of metastatic disease and allow for appropriate modifications to the recommended treatment regimen. We currently favor maximal safe resection of the most readily accessible tumor when possible and when not possible, a biopsy prior to treatment followed by adjuvant carboplatin/vincristine treatment. In patients with progressive disease, salvage therapy may be effectively achieved with further chemotherapy and/or radiation therapy, and a molecular analysis of the tumor should be performed for actionable mutations when possible.

Conclusions

Primarily metastatic JPA is uncommon and its long-term outcomes have not previously been described. Based on our institutional experience, we found that many patients with primarily metastatic JPA will have stable disease after upfront treatment, although the higher rate of stable disease found in this series relative to other reports is likely the result of the small sample size.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Grant, Yecies. Acquisition of data: Yecies. Analysis and interpretation of data: Grant, Yecies. Drafting the article: Yecies. Critically revising the article: Grant, Yecies. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Grant. Administrative/technical/material support: Fisher, Cheshier, Edwards.

Supplemental Information

Previous Presentations

Portions of this work were presented at the meeting of the Western Neurosurgical Society, Sun Valley, Idaho, 2014.

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