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Incidental Diagnosis of Diffuse Intrinsic Pontine Glioma in Children

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Abstract

Children with diffuse intrinsic pontine glioma (DIPG) have a short onset, rapidly progressive neurologic decline before diagnosis. Therefore, incidental diagnosis of such an aggressive cancer is counterintuitive, yet our experience shows DIPG may occur as part of a spectrum of incidentally diagnosed pediatric brain cancers. Although children with incidentally diagnosed DIPG may experience a longer survival, it remains a potentially deadly cancer despite treatment with radiotherapy. Histologic confirmation is warranted when feasible in such patients to confirm diagnosis. Moreover, recent advances in genome-wide analyses may suggest incidentally diagnosed DIPGs are biologically distinct from the majority of these cancers.

Keywords

Pediatric hematology/oncology; tumor biology; neuro-oncology

Introduction

The widespread availability of CT and MRI provide the ability to detect asymptomatic abnormalities in the brain, ranging from conditions without clinical significance to those requiring immediate medical care, including brain tumors [1,2]. Diffuse intrinsic pontine glioma (DIPG), the most lethal pediatric brain cancer, causes rapid, progressive pyramidal deficits, cranial nerve palsies, and cerebellar signs after short intervals, usually less than one

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month [3,4]. Therefore, the incidental diagnosis of such an aggressive cancer is counterintuitive. We report a series of children with incidentally diagnosed DIPG.

Methods

After obtaining Institutional Review Board approval, we reviewed the clinical and radiologic characteristics of patients with incidentally diagnosed DIPG treated or seen in consultation from July 2002 until June 2013. Incidental diagnosis was defined as the unexpected discovery of DIPG by brain imaging obtained for reasons unrelated to the diagnosis of a brain tumor. Brain MRIs of all affected patients were reviewed by a neuro-radiologist to confirm typical characteristics consisting of primary pontine tumors involving more than 50% of this segment and exerting mass effect on surrounding structures [5].

Results

Three of 146 patients seen at our institution during the study period had an incidentally diagnosed DIPG. The median age of patients without incidentally diagnosed DIPGs was 6.2 years (range: 1.1 to 17.3 years).

Reasons for undergoing initial brain imaging for those patients incidentally diagnosed consisted of traumatic head injury with skull fracture (patient 1) [6], meningococcal meningitis with septicemia (patient 2), and suspected head trauma following a motor vehicle accident (patient 3). None of the patients had symptoms and/or signs attributable to brainstem involvement at diagnosis, which was independently confirmed by a pediatric neuro-oncologist and neurologist. None of the patients had neurofibromatosis type 1.

Brain MRI at diagnosis showed typical characteristics of DIPG in all three patients (Table I and Fig. 1). Only patient 3 underwent a stereotactic needle biopsy of the tumor at diagnosis following a lateral occipital approach through the middle cerebellar peduncle. At least five representative tumor samples were taken from multiple surrounding areas. The biopsies were taken from an area posterior to the basilar artery which showed increased restricted diffusion, hyperperfusion, and some occult post contrast enhancement suggesting a more aggressive portion of the tumor [7]. Pathology was consistent with diffuse astrocytoma (WHO grade II). Gene sequencing showed no mutations at K27 or G34 in *H3F3A* or at K27 in *HIST1H3B* [8]. Twelve of 143 patients in the control cohort underwent histologic confirmation at biopsy and 37 patients at autopsy. One patient had both a biopsy at diagnosis and autopsy at the time of death. The histologic diagnoses consisted of grade 2 astrocytoma ($n=3$), anaplastic astrocytoma ($n=3$), high grade glioma ($n=6$) and glioblastoma multiforme ($n=38$).

Patient 2 required a third ventriculostomy at diagnosis because of hydrocephalus. Patients 1 and 2 did not receive any anticancer therapy (radiotherapy) for 9 and 15 months after diagnosis until they experienced radiologic and clinical progression, respectively. Patient 1 also received erlotinib (Tarceva[®], Astellas Pharma, Northbrook, IL; Roche, Basel, Switzerland; Genentech, South San Francisco, CA) during and after radiotherapy [6]. Patient 3 underwent local radiotherapy following histologic confirmation. Patients 1 and 2 died of tumor progression 30 and 31 months after diagnosis, respectively. Patient 3 remains alive,

free of tumor progression 30 months after diagnosis (Table I). The median survival for the control cohort ($n=143$) was 7.2 months (range 0-11.2 years).

Discussion

The incidental diagnosis of mostly low-grade brain cancers in children and adults was previously reported, including a few cases of brainstem tumors [1,2]. Two of those incidentally diagnosed brainstem tumors were tectal plate gliomas, which are notoriously indolent cancers [2]. A third case consisted of an infiltrative brainstem tumor that was followed without anticancer therapy for 46 months [2]. No further details were provided whether this later case met the radiologic criteria for DIPG or whether histologic confirmation was obtained. A few cases of incidental, high-grade brain cancers have also been reported in children [2].

The decision to pursue histologic confirmation and/or to treat children with incidental brain cancers is controversial [2]. These issues are particularly more challenging when incidental brain cancers affect young children and/or involve critical structures such as the brainstem. Our first two patients did not receive radiotherapy until they experienced disease progression because of their young age. Young age and lack of florid neurologic deficits, particularly cranial nerve palsies, are associated with improved prognosis in children with DIPG [3-5]. Patient 3 underwent immediate radiotherapy based on the fatal outcome of our two initial patients. The finding of a fibrillary astrocytoma with a wild-type *H3F3A* in patient 3 was not surprising since low-grade gliomas account for a subset of radiologically typical DIPGs and the lack of K27M H3.3 mutations seem to be associated with an improved prognosis [9].

Our experience suggests that DIPG is part of the spectrum of incidentally diagnosed pediatric brain cancers. As we showed, incidentally diagnosed DIPGs remain potentially deadly cancers. No conclusions can be drawn whether immediate therapy is warranted in such cases based on our experience. However, we recommend biopsy of incidentally diagnosed DIPGs, particularly when performed by experienced neurosurgeons in the context of clinical trials, not only for histologic confirmation but also to perform molecular studies. DIPGs are molecularly heterogeneous, yet up to 80% of cases harbor histone mutations [9, 10]. Some of these mutations (e.g., K27M *H3F3A* mutation) seem to be associated with worse prognoses [8]. Similar to our patient 3, all long-term survivors of DIPG in another report had a wild type *H3F3A* [9].

The very rare, incidentally diagnosed DIPGs could be simply due to early detection of such tumors before patients become symptomatic due to widespread availability of brain imaging. On the other hand, incidentally diagnosed DIPGs could represent a subset of tumors enriched with molecular characteristics associated with less aggressive growth. The long interval time (9 and 15 months) between confirmation of radiologically typical tumors and start of anticancer therapy due to disease progression in patients 1 and 2, and the lack of histone mutations in patient 3, a characteristics only found in the minority of DIPGs, suggests that the second possibility may be more plausible. However, additional studies are needed to support this hypothesis.

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Figure 1. Sagittal and axial T₂-weighted images of the brain for patients 1 (A and B), 2 (C and D), and 3 (E and F) demonstrate hyperintense lesions that involve nearly the entire pons (arrows) with encasement or partial encasement of the basilar artery (arrowheads). There is associated effacement of the prepontine and cerebellopontine angle cisterns.

Table 1
Clinical Characteristics at Presentation, Treatment, Outcome and MRI Findings

Patient	Age (year)/Gender	Indication for brain imaging	MRI finding				Interval between diagnosis and therapy (months)	Therapy		Survival from diagnosis
			Tumor dimensions (cm3: T × AP × CC)	T1 signal intensity	T2 signal intensity	Enhancement following gadolinium administration		Local RT (54 Gy)	Chemo	
1	2.2/F	Head trauma	4.5 × 3.1 × 4.5	Hypo-intense	Hyper-intense	No	9	Yes	Yes (erlotinib)	30
2	3.6/M	Menigococcal meningitis and septicemia	4.9 × 3.3 × 4.2	Hypo-intense	Hyper-intense	Minimal	15	Yes	No	31
3	16.8/F	Motor vehicle accident	4.6 × 3.4 × 3.6	Hypo-intense	Hyper-intense	Minimal	1	Yes	No	28

F, female; M, male; T, transverse; AP, antero-posterior; CC, cranio-caudal; RT, radiation therapy; Gy, Gray; Chemo, chemotherapy.