Diffuse Intrinsic Pontine Glioma in Children: Document or Treat?

Beuriat Pierre-Aurélien[1], Szathmari Alexandru[1], Di Rocco Federico[1], Kanold Justyna[3-5], Mottolese Carmine[1], Frappaz Didier[2]

Key words
- Biopsy
- Complications
- Diffuse intrinsic pontine glioma
- Pediatric

Abbreviations and Acronyms
DIPG: Diffuse intrinsic pontine glioma
MRI: Magnetic resonance imaging
RT: Radiotherapy

From the [1]Department of Pediatric Neurosurgery, Hôpital Femme Mère Enfant, Lyon Cedex; [2]Pediatric Institutes of Haematology-oncology, Lyon; [3]Pediatric Haematology and oncology unit, University Hospital, Clermont-Ferrand; [4]INSERM-CIC 1405, CRECHE unit, Clermont-Ferrand; and [5]Auvergne University, Clermont1 University, Faculty of Medicine, Clermont-Ferrand, France

To whom correspondence should be addressed: Beuriat Pierre-Aurélien, M.D. [E-mail: pierre-aurelien.beuriat@neurochirurgie.fr]

Citation: World Neurosurg. (2016) 93:485.e11-485.e14. http://dx.doi.org/10.1016/j.wneu.2016.07.011

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

BACKGROUND: **The place of stereotactic biopsies in the management of diffuse intrinsic pontine gliomas (DIPGs) in children has changed over the years. Nonetheless, stereotactic biopsy remains a surgical procedure with its risks. One complication that has not been reported previously in case of a biopsy of a DIPG is metastatic seeding along the tract of the biopsy. We report the first 2 cases in the literature.**

CASE DESCRIPTION: **One 8-year-old and one 9-year-old boy were admitted for a typical DIPG. Parents choose to be included into a research protocol that required a stereotactic biopsy. The biopsy was performed in both cases without any intraoperative complications, and they both received their treatment according to protocol. Unfortunately, 3 and 1 months respectively after the biopsy, their clinical condition deteriorated. MRI showed a metastatic seeding along the tract of the biopsy, and both patients died of disease progression.**

CONCLUSIONS: **The era of targeted therapy with molecular and genomic discoveries has paved the way to a research protocol that requires a biopsy from the patient. The reported complications have never been described before. The purpose of this paper is not to suggest that no biopsy should be performed when a DIPG is suspected. For now, biopsy remains investigational, because no benefit in survival could be drawn so far for any patient. This subject deserves honest discussion with the children and their parents.**

INTRODUCTION

Diffuse intrinsic pontine gliomas (DIPGs) represent up to 15% of all the childhood tumors of the central nervous system and 80% of the tumors that arise from the brainstem. Unfortunately, the median of survival remains less than 1 year.[1] No real improvement in the management of DIPGs has occurred for the last few decades.[2,3] Stereotactic biopsies have regained acceptance among the neurosurgical community, with the advent of the era of targeted therapy protocol that requires a histologic, molecular, and genomic analysis in the workup of a patient; however, it remains a surgical procedure with risks, even if major technical improvements has been made and a lower rate of complications has been described.[4] One complication that has never been reported in case of a biopsy of a DIPG is metastatic seeding along the tract of the biopsy. Here, we report the first 2 cases in the literature.

CASE 1

An 8-year-old boy with no personal or family medical history presented with progressive walking difficulties lasting a few weeks. Findings of a neurologic examination revealed left hemicorporal hemiparesis predominating at the lower limb; however, the patient was able to walk unassisted. He had neither sensitive disorders nor signs of intracranial hypertension. There were no cranial nerve deficits, particularly no facial paresis or swallowing difficulties.

He was referred immediately for a craniospinal magnetic resonance imaging (MRI). Axial T2-weighted images showed an enlargement and hypersignal of the pons. Axial T1-weighted images showed an enlargement and hyposignal of the pons. Postgadolinium contrast T1-weighted images showed multifocal nodular central enhancement (Figure 1A–B). Spectroscopy showed a decrease in n-acetyl aspartate and an elevation of choline and myo-inositol. The lesion was localized to the pons with no brain or cerebellar metastasis. MRI of the spinal showed no medullary metastasis. The clinical presentation and the MRI findings were in favor of a DIPG.

The parents were informed of all the different therapeutic options, including upfront standard radiotherapy (RT) without biopsy and inclusion into a research protocol (BIOMED Protocol No: CSET2014/2126 EudraCT No: 2014-001929-32), which required a stereotactic biopsy. They could choose which option they preferred. In this case, the parents choose the research protocol option and signed the informed consent form. Therefore, a stereotactic biopsy was performed. No intraoperative complications were observed. The results of a histologic study confirmed the diagnosis of DIPG with loss of H3K27me3 trimethylation, K27M H3.3 mutation, and a loss of

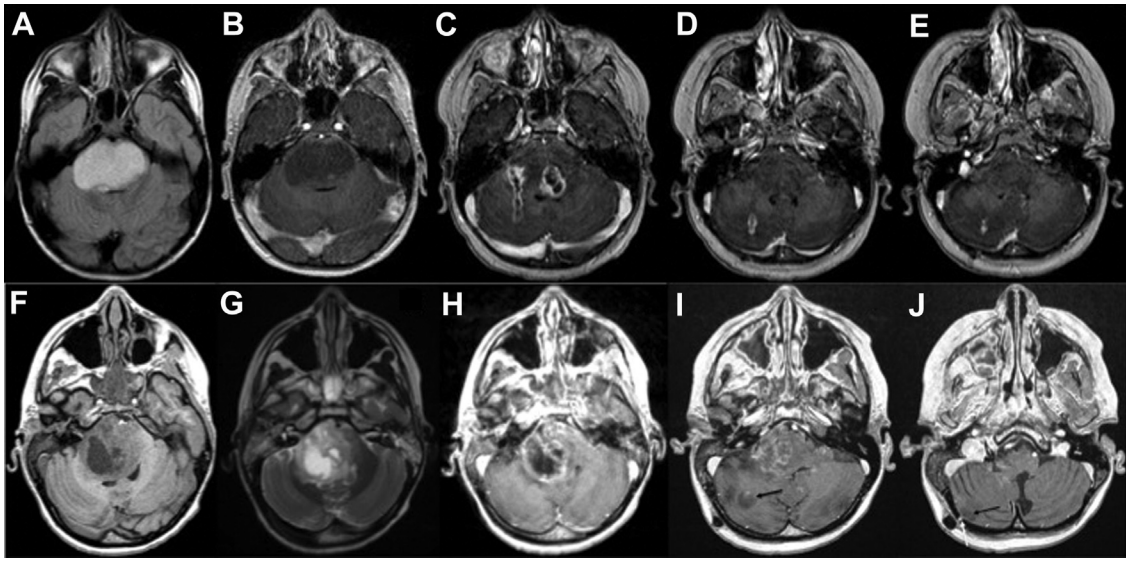

Figure 1. Patient 1. (**A**) Preoperative magnetic resonance imaging (MRI) in an axial fluid-attenuated inversion recovery (FLAIR) T2-weighted image of a DIPG showing a typical hypersignal and enlargement of the pons. (**B**) Preoperative MRI in an axial T1-weighted, contrast image of a diffuse intrinsic pontine glioma (DIPG) showing a strictly local disease (hyposignal with a little enhancement in the pons) with no metastasis into the posterior fossa. (**C**–**E**) Late postoperative MRI in an axial T1-weighted, contrast image showing the contrast enhancement along the trajectory of the stereotactic biopsy. **Patient 2**. (**F**) Preoperative MRI in an axial T1-weighted image of a DIPG showing a typical hyposignal and enlargement of the pons. (**G**) Preoperative MRI in an axial FLAIR T2-weighted image of a DIPG showing a typical hypersignal and enlargement of the pons. (**H**) Preoperative MRI in an axial T1-weighted, contrast image of a DIPG showing a strictly local disease (hyposignal with a little enhancement in the pons) with no metastasis into the posterior fossa. (**I**–**J**) Late postoperative MRI in an axial T1-weighted, contrast image showing the contrast enhancement along the trajectory of the stereotactic biopsy (*black arrows*). Note the contrast enhancement of the dura at the level of the biopsy entry (*white arrow*).

PTEN expression. The patient was included into the BIOMEDE protocol and randomized in the group with concomitant everolimus (mammalian target of rapamycin inhibitor) and RT. He completed the entire RT protocol of 54 Gy in 30 fractions of 1.80 Gy. No complications were reported. Everolimus was maintained after the end of RT.

Unfortunately, the patient's clinical condition rapidly deteriorated within 3 months after the end of RT. MRI showed a local progression of the tumor with metastatic seeding along the tract of the biopsy (Figure 1C–E) and no spinal metastasis. A multidisciplinary team meeting advised to start bevacizumab (antivascular endothelial growth factor). Transient improvement of his medical condition and on MRI was noted. The patient died of progressive disease 12 months after the initial diagnosis.

CASE 2

A 9-year-old boy with no personal or family medical history was addressed by his general practitioner for a 2-month history of unexplained falls and apparition of a diplopia. Findings of the neurologic examination showed a cerebellar syndrome with ataxia. He had neither sensibility disorder nor signs of intracranial hypertension. There was a right sixth nerve palsy but no facial paresis or swallowing difficulties. He was referred for a craniospinal MRI. The clinical presentation and the MRI finding (Figure 1F–H) were in favor of a DIPG.

The parents were informed of the different therapeutic options, including upfront standard RT without biopsy and inclusion into a research protocol (BIOMED Protocol No.: CSET2014/2126 EudraCT No.: 2014-001929-32), which required a stereotactic biopsy. They could choose which option they preferred. The parents choose the research protocol option. Therefore, a stereotactic biopsy was performed. No intraoperative complications were noted. Findings of a histological study confirmed the diagnosis of DIPG with loss of H3K27me3 trimethylation, K27M H3.3 mutation, and a loss of PTEN expression. Therefore, he was included into the BIOMEDE protocol and randomized in the group with concomitant dasatinib (platelet-derived growth factor inhibitor) and RT. He completed the entire RT protocol of 54 Gy in 30 fractions of 1.80 Gy. No complications were reported. Dasatinib was maintained after the end of RT.

Unfortunately, the patient's clinical condition rapidly deteriorated within 1 month after the end of RT. MRI showed local progression of the tumor with a metastasis along the tract of the biopsy (Figure 1I–J), hydrocephalus, but no spinal metastasis. A multidisciplinary team meeting advised to start bevacizumab (antivascular endothelial growth factor). He also benefited from the placement of a ventriculoperitoneal shunt. Transient improvement of his medical condition and on MRI was noted. The patient died of progressive disease 11 months after the initial diagnosis.