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Case Report
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Diffuse Midline Glioma, H3 K27M-Mutant of the Pons-Multidisciplinary Approach

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Abstract

Background: Diffuse Midline Glioma (DMG) H3 K27M-mutant of the pons is the most common pediatric brainstem tumor, leading to poor outcome. Radiotherapy is the only proved therapeutic option that offers temporary benefit, while co-adjuvant chemotherapy is still controversial. Although MRI allows for the diagnosis of DMG, biopsy is the gold standard as it offers additional molecular biology information that can be useful for future targeted immune or chemotherapy.

Case Report: A 6-year-old girl presented with a 6 months history of vomits, ataxia with frequent falls, left peripheral facial palsy and headache plus irritability. Brain MRI showed an intra-axial lesion in the mesencephalon and pons, hypointense in T1, hyperintense in T2 and FLAIR, without contrast enhancement. The dysmorphic pons partly surrounded the basilar artery, obstructing the upper part of the 4th ventricle and aqueduct, with supratentorial ventricular dilatation. A transfrontal stereotactic biopsy of the lesion was performed followed by an Endoscopic Third Ventriculostomy (ETV). Histology and biology confirmed the diagnosis of H3 K27M-mutant DMG.

Conclusion: Biopsy is an invasive procedure – however, it should be offered to children with presumptive imaging of DMG. It shows low morbidity, confirms the diagnosis and has potential utility for research on targeted chemotherapy or immunotherapy for secondary treatment approach.

Keywords: Diffuse midline glioma; Stereotactic biopsy; Molecular diagnosis; Targeted chemotherapy

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Introduction

Diffuse Midline Glioma (DMG) H3 K27M-mutant of the pons is a rare malignant brain tumor of childhood, the most common subtype (80% to 85%) among diffuse midline gliomas [1,2]. Despite decades of research, the outcome remains dismal: overall survival is 9 to 12 months, with less than 10% of patients alive at 2-years follow-up [3-5]. Most patients present with signs and symptoms of brainstem dysfunction [6] with 22% to 89% developing obstructive hydrocephalus [7]. The classic triad includes ataxia, long tract signs and multiple cranial nerves deficits. A rapid progression is usually observed, with symptoms evolving over 1 to 2 months [5]. DMG presents on MRI as a lesion which typically occupies two thirds of the pons, showing hypointensity in T1 and hyperintensity in T2. A grim survival correlates with contrast enhancing [8,9]. Encasement of the basilar artery is a classic feature of DMG, and it may also protrude into the aqueduct/fourth ventricle, causing hydrocephalus. For decades, the topography of DMG coupled with typical MRI characteristics based the diagnostic criteria enough to perform therapy. This diagnostic approach led to an insufficient insight into the molecular pathogenesis of DMG. The paradigm started changing in the late 1990'swith Puget et al. [10], that questioned the lack of safety of biopsies in the brainstem needed to obtain useful clinical biomarkers, an assessment corroborated by other authors [11,12]. Radiotherapy still remains the cornerstone of DMG treatment with little progress towards effective chemotherapy [4,13,14]. We report on the clinical case of a patient that underwent biopsy of DMG,

with focus on surgical technique and risks, results of histologic and molecular studies, ongoing therapies and review of current evidence.

Case Presentation

A 6-year-old girl presented with 6 months of headache, vomits, ataxia and left peripheral facial palsy along with irritability in the days prior to admission. Her mother reported an increasing number of falls in that period without objective motor deficit. ACT scan made three months prior showed no evidence of intracranial lesions. Brain MRI revealed an intra-axial lesion in the pons and mesencephalon, hypointense in T1, hyperintense in T2 and FLAIR (Figure 1), without contrast enhancement, partly encasing the basilar artery without stenosis, and compressing the aqueduct/4th ventricle with slight ventricular dilatation. No cerebellar tonsil herniation was found, neither were other lesions on whole-spine MRI. Considering a probable diagnosis of DMG, it was decided to undertake a transfrontal stereotactic brainstem biopsy (Leksell® frame, Elekta AB®, Stockholm, Sweden). The biopsy was planned through a volumetric FLAIR and T1-Gadolinium imaging merged with the stereotactic CT protocol on the workstation (Stealth Station S8, Medtronic®, Dublin, Ireland) (Figure 2). The target was a small area with diffusion restriction to avoid under sampling. Stereotactic biopsy was done through a right-sided frontal burr hole, with collection of three tumor fragments *via* a Sedan needle, without apparent bleeding. Secondly, an Endoscopic Third Ventriculostomy (ETV) was performed (Minop® system, optics 0 degrees, AesculapInc; Tuttlingen, Germany) that also allowed the collection of 10 cc of CSF for standard study (cytology, biochemistry work, microbiology), tumoral germinative markers (β-HCG and α-fetoprotein) and molecular studies. The procedure was uneventful, with the child presenting no new neurological deficits. Control CT scan did not reveal adverse events -the child was transferred from the Pediatric ICU to the Pediatric Oncology ward on day one post-operative. She displayed less irritability when compared to pre-ventriculostomy status. Histology and biology examination confirmed Diffuse Midline Glioma, H3 K27M-mutant (Figure 3). The molecular study was performed using the NGS panel Oncomine TM Childhood Cancer Research Assay to search for molecular alterations at the DNA and RNA level: p. (Lys27Met) in HIST1H3B, p. (Cys135Gly) in TP53, and p. (Gly328Trp) in ACVR1were found to be mutated. No gene rearrangements or CNVs were found. After surgery, steroids were discontinued and the patient started complementary therapy– a 12-week induction cycle of Nimotuzumab 150 mg/m^2 and Vinorelbine 20mg/m^2 once per week, followed by a maintenance scheme with both drugs (Vinorelbine increased to 25 mg/m^2), once every 2 weeks, up to 52 weeks or progression. Three weeks into induction, the child started

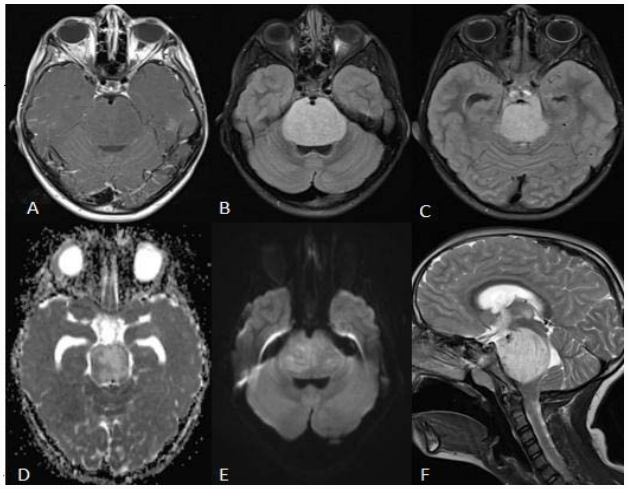

Figure 1: Intra-axial ponto-mesencephalic lesion, hypo/isointense in T1 (A), hyper intense in T2 and FLAIR (B,C), with foci of restriction to diffusion (D,E). The basilar artery is almost completely encased by the tumor, as it ascends in the interpeduncular fossa. There is marked compression of both the aqueduct and 4th ventricle, with subsequent supratentorial ventricular dilation.

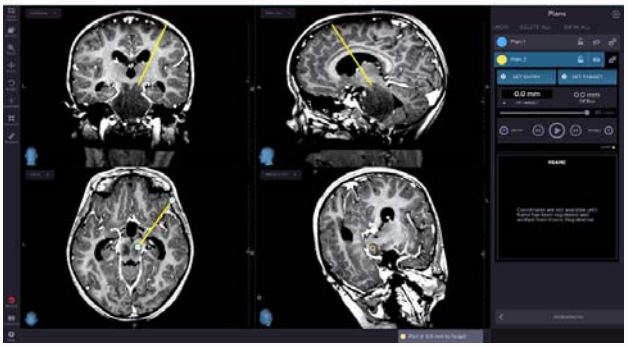

Figure 2: Surgical planning for the biopsy – target set for lesion on the right side of the mesencephalon, attempting to avoid lemnisci, periaqueductal nuclei, and medial longitudinal fascicle. A small area with diffusion restriction was chosen as target to avoid under sampling.

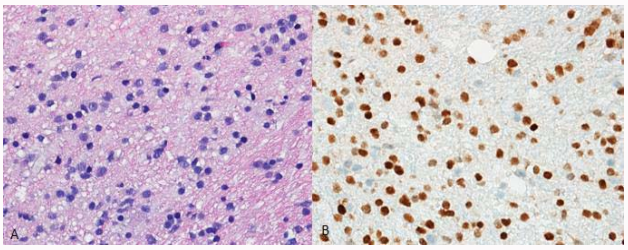

Figure 3: Diffuse glioma with monomorphic tumor cells (3A**:** 400x – HE). Strong nuclear staining for K27M-mutant H3 is present in tumoral cells (3B: 400x).

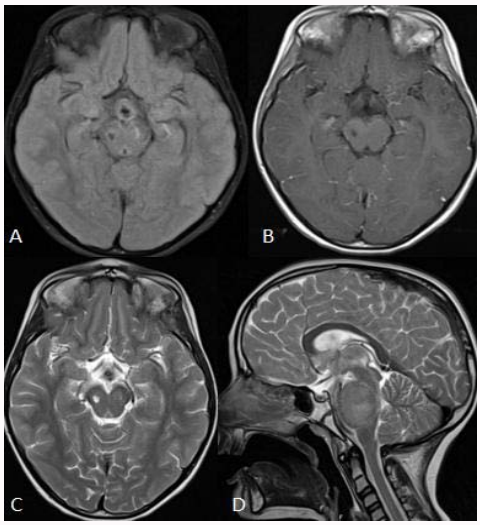

Figure 4: At 4 months after biopsy, and after complementary therapy, the tumor was reduced in size, with no foci of enhancement after gadolinium, less edema and no hydrocephalus. Basal cisterns are less compressed, and the basilar artery is less engulfed by the tumor. Significantly, there is minimal local impact from the biopsy on the right side of the mesencephalon.

local radiotherapy 54 Gy in 30 fractions of 1.8 Gy/day over 6 weeks with 3DCRT technique [15,16]. She tolerated the treatment well in an outpatient setting (despite a brief pause for an asymptomatic SARS-COV2 infection), with both clinical and image improvement, without need for VP shunt at seven months of follow-up (Figure 4).

Discussion

DMG is uniformly associated with a poor outcome, with survival rates ranging from 9 to 12 months [5]. A management strategy based for a long time on MRI findings in detriment of histological diagnosis led to decades of delay in molecular biology knowledge [17]. The main argument against biopsy was the high risk of complications in procedures of the pons and mesencephalon. It was argued that it was not cost-effective to risk morbidity from this invasive procedure in patients whose MRI features were considered typical [18,19]. However, Kickingereder et al. [11] reported 7.8% of morbidity in their meta-analysis of 1,480 stereotactic biopsies of brainstem tumors (transfrontal and transcerebellar approaches) with only 1.7% of permanent deficits. Debate over the best route is still ongoing. Dellaretti et al. reported slightly higher success rates with transfrontal *vs.* transcerebellar approaches (95.1 *vs.* 84.2%), but with similar low morbidity [19]. Usually, a transfrontal approach is chosen for lesions in the mesencephalon, while transcerebellar tends to be preferred for pontine lesions [20-22]. Gonçalves-Ferreira et al. [21] described that the angle of the tentorium made the mesencephalon more easily accessible through a transfrontal approach. This author also pointed that the transcerebellar approach was the shortest route for the pons but was associated with a higher risk of complications [21]. Biopsy precision can be improved with fusion of MRI images with pre-operative CT scan, avoiding eloquent areas while increasing tissue biopsy yield [23-26]. Some author's caution against potential errors during registration and fusion of images, amenable to correction in the workstation [27]. The role of PET scan for biopsy planning is still under study. Goda et al [28] reported efficacy in detecting high-grade tumors with 18F-FDG, but sensitivity below 50% for low-grade brainstem tumors. Kossatz et al. [29] describes that 18F-PARPi may hold greater potential in aiding planning of a biopsy, but more studies are required. Lack of availability of the original CT scan made 3 months prior to admission prevents a retrospective re-assessment– but its description as without lesions signals the low sensitivity of CT to DMG.

Tissue biopsy allowing pathology and molecular studies could be the key in reversing the unfavorable prognosis of DMG. Histone H3 gene mutations are among the most common, affecting regulation of gene transcription and DNA methylation [30]. K27M mutation in H3F3A, HIST1H3B and HIST1H3C genes is used to classify these tumors according to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System, being present in over 80% of DMG patients [30,31]. Detection of the H3K27M mutation in CSF cytology is under study, underlining the importance of collecting CSF samples [30]. The case here reported harbors the K27M hotspot mutation in HIST1H3B, which is usually observed in 25% of DMG patients [32]. This mutation was found together with the G328W in ACVR1, a hotspot gain-of-function mutation intimately associated with the HIST1H3B K27M in DMG. The tumor also showed a TP53 mutation, which is a common finding, particularly in H3F3A-mutant DMG S. Targeting oncogenic transcription with bromodomain inhibition, blocking CDK7 or using inhibitors of ALK2 (encoded by ACVR1 gene) may lead to new therapies that could improve survival outcomes [34,35]. Li et al. found that 6 out of 11 DMG patients presented with over expression of EGFRvIII, a surface molecule rarely present in normal tissue [36-38]. This has led to the inclusion of nimotuzumab, an anti- EGFR monoclonal antibody, in DMG chemotherapy regimens. Massimino et al. [16] described improved outcomes with the addition of nimotuzumab to vinorelbine and radiotherapy (response in 96% of patients, PFS and OS of 30 ± 10% and 76 ± 9% at 1 year, respectively; at 2 years, OS was 27 ± 9%). Our multidisciplinary group used the same regimen described by Massimino et al. [16], with our patient displaying a favorable progression thus far. Its use in an outpatient setting is associated with very few side effects and great tolerability. Thus, sharing histological and molecular results with multicentric DMG registries (International DIPG Registry (IDIPGR), European Society for Pediatric Oncology DIPG Registry (SIOPE-DIPGR) will help overcome the rarity of this tumor and years of delay in research [39,40].

A crucial procedure which may improve the clinical status in DMG patients is the treatment of obstructive hydrocephalus [7]. Fonseca et al. [41] describes that up to 55% of DMG patients may present with ventriculomegaly. The majority are asymptomatic and do not require surgical treatment. However, in the group that becomes symptomatic, CSF diversion improves survival outcomes [41]. The role of ETV in this subgroup is well established, as is both safe and effective in the pediatric population. Guida et al. [42] in their systematic review of 6 studies reported 86% (30/35 patients) of sustained clinical improvement with ETV in DMG patients, with no associated morbidity. Considering the poor overall prognosis, it is important to treat these patients early and assertively. The uneventful course of the case described above allowed an early start of adjuvant treatments, a key goal for choosing minimally invasive procedures. The possibility of shortening duration of corticosteroids therapy is an important additional advantage, enabling better efficacy of complementary treatment, both chemo and radiotherapy, while avoiding well-known negative effects.

Conclusion

Stereotactic brainstem biopsy is safe and should be considered in suspected DMG on MRI. Planning for the stereotactic procedure with neuronavigation using MRI-CT fusion increases precision of tissue sampling and lowers the morbidity of the procedure, resulting in increased effectiveness. Histological and molecular diagnosis is of high importance to understand the pathogenesis and unravel more effective targeted therapies against DMG.

Contributions

RR is the main author and wrote the article. BC and JP planned and implemented the procedure. LS provide image diagnosis, MJGC, SS and LO provided support and complementary treatment. RS provided support regarding histology. JL provided molecular studies. RV and JP contributed to the intellectual concept of the article. All authors review the manuscript.

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