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Does Simultaneous Intensity Modulated Radiotherapy with Temozolomide Increase the Radiosensitivity of Childhood Diffuse Intrinsic Pontine Glioma (DIPG)?- a Clinical Case from our Practice

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ABSTRACT

Diffuse intrinsic pontine glioma (DIPG} is a high-grade glioma (HGG) that originates in the pons and is seen almost exclusively in children. The healing results achieved after a self -conducted conventional, hyperfractionated and hypofractionated radiotherapy (RT) up to a total tumor dose of 54 Gy at DIPG are unfavorable. We present our observations in a child with a locally advanced DIPG after a conventional concomitant Temozolomide radiotherapy. In order to increase the survival in this clinical case, we decided to conduct a simultaneous Temozolomide RT with an extended target volume with the inclusion of the ventricles. Two months after the Temozolomide intensity modulated radiotherapy (IMRT), the MRI reports a reduction in the tumor with a pronounced tumor necrosis, which is evidence of the radio -sensitization effect of Temosolomide.

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Introduction

The number of children with high-grade gliomas (HGG) is much smaller than the number of adults with these neoplasms. Whereas 40%–50% of all pediatric CNS tumors are gliomas, supratentorial high-grade astrocytomas constitute only 6%–12% of all primary pediatric brain tumors, and diffuse brainstem gliomas constitute only 3%–9% [1]. As with adults, HGG in children may occur anywhere in the central nervous system (CNS). However, in children, there tends to be a greater percentage of tumors that are localized in the deep gray matter, cerebellum, and especially within the brainstem [2]. Despite recent advances in diagnostic techniques and in therapies used to treat pediatric brain tumors, little progress has been made in increasing the survival rates of children with supratentorial high-grade astrocytomas and diffuse brainstem gliomas [3]. Conventional radiotherapy (RT) with a dose of 54 Gy remains the only proven therapeutic option [4]. Due to the adverse healing results, we present our observations in a child with a locally advanced DIPG after combined with Temodal conventionally fractionated IMRT.

Clinical Case

It concerns an 8-year-old child. For several weeks, the mother noticed a disturbed gait, staggering and loss of balance, as well as a distorted gaze. After an MRI of the head, a formation in the area of the pons with occlusive hydrocephalus was found, which required emergency admission to the Neurosurgery Clinic for diagnostic clarification and placement of a ventriculoperitoneal shunt. Neurological status- A large inexhaustible nystagmus was found when looking to the right and a positive nasal swab with intention tremor and dysmetria. Tendon-periosteal reflexes - bilaterally very strong with positive Achilles. A brain MRI is required.

MRI from 17.05. 2024 before ventriculoperitoneal shunt placement - MR data of an intraaxial tumor involving the mesencephalon, pons, medulla oblongata and left middle cerebellar peduncles. The formation is located in the middle and more to the left. The finding inflates the involved brain structures and fills the prepontine and left pontocerebellar cisterns. The formation has a heterogeneous structure and the presence of a cystic component. The fourth ventricle is compressed and displaced dorsally and to the right. Among the introduction of the contrast, the formation increases its signal inhomogeneously and weakly. In the left cerebellar hemisphere, a second round intraaxial lesion with a signal characteristic identical to the one described above was visualized. Both lateral and third ventricles are symmetrically dilated with evidence of transependymal resorption. Conclusion- The described intraaxillary lesion in the brainstem of the highest degree can be associated with a primary glial tumor and evidence of triventricular occlusive hydrocephalus.

MRI after placement of ventriculoperitone shunt - MP data on intraaxial tumor engaging the mesencephalone, ponscies, medulla grain and left medium -sized short -term feet. The formation is located medium and more to the left. The find inflates the engaged brain structures and fills and fills the Spiritual and Left Pontocerebellar Tanks. No data on occlusive internal and external hydrocephalus (Figure 1).

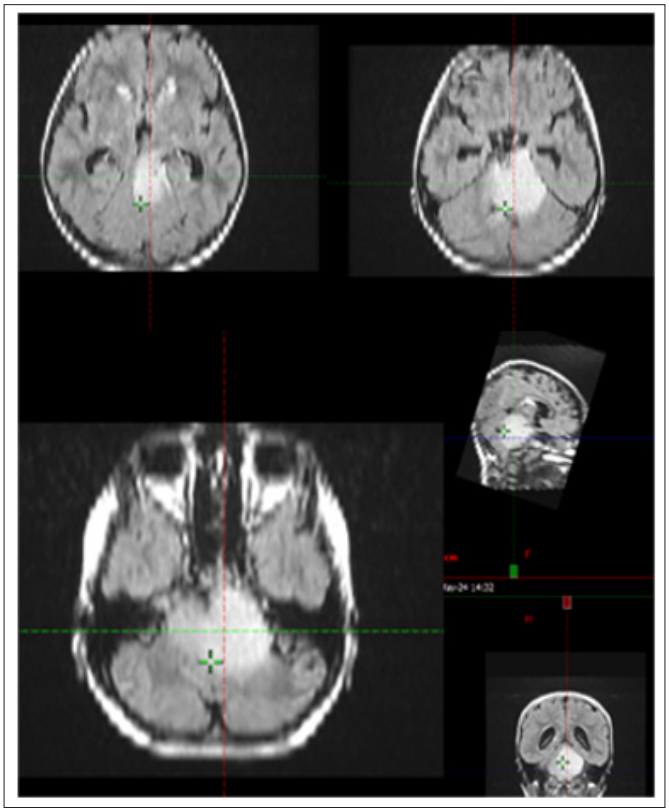

Figure 1: MRI after ventriculoperitoneal shunt placement - MR data of an intraaxial tumor involving the mesencephalon, pons, medulla oblongata and left middle cerebellar peduncles. The formation is located in the middle and more to the left.

The child was referred for definitive RT, which we decided to carry out in combination with Temodal/Temozolomide tablets orally at a dose of 76 mg/m^2 throughout the radiotherapy cycle for 42 days. The necessary hematological criteria were met: absolute number of neutrophil granulocytes ≥ 1.5 x 10 ^{9}/l, platelets ≥ 100 x 10 ^{9}/l. Against the background of 4 mg of Dexamethasone daily, the child underwent intensity modulated radiation therapy (IMRT) according to the VMAT method in the tumor area (GTV) with coverage zone (CTVp) using 30 fractions with a daily dose (DD) of 1.8 Gy up to total dose (TD)) 54 Gy, and simultaneously in the ventricles (CTVventr) with DD 1.6 Gy up to TD 48 Gy. (Figure 2, Figure 3) IMRT was suffered without acute hematological and neurological toxicity. During the radiation, we have conducted once a week of eye status tracking. *Eye bottoms during combined radiation*- The optic disc vital with clear borders. Retina, macula and vessels normally. Papilla -vital with clear boundaries.

After completion of RT, the child was referred to a pediatric oncologist for subsequent Temodal monotherapy. Four weeks after the completion of radiotherapy combined with Temodal, Temodal was started as monotherapy for a maximum of 6 cycles. The dose in Cycle 1 (monotherapy) is 150 mg/m^2 once daily for 5 days, followed by 23 days without taking Temodal. At the beginning of Cycle 2, the dose is increased to 200 mg/m^2, After two months of completing the combined IMRT, a follow-up MRI was performed in September 2024 (Figure.4). The child continues monotherapy with Temodal, undergoing a follow-up MRI after 4 months.

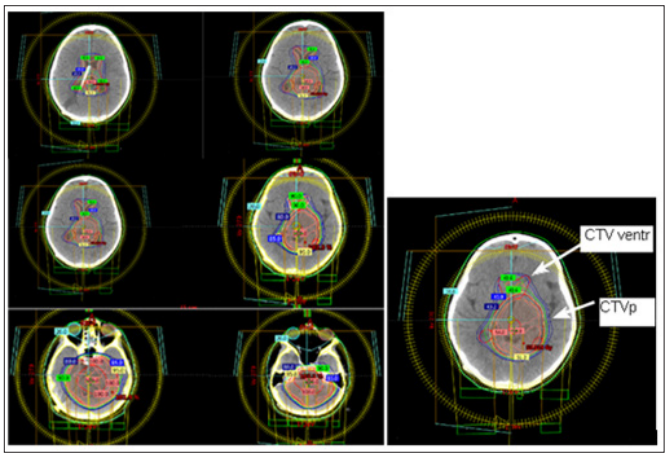

Figure 2: Target volumes - GTV and CTVp, as well as cerebral ventricles / CTV ventr.

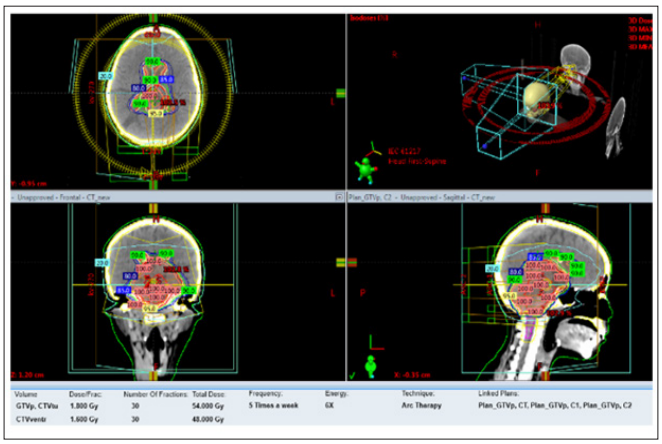

Figure 3: Intensity modulated radiotherapy (IMRT) according to the VMAT method in the tumor area (GTV) with coverage zone (CTVp) using 30 fractions with a daily dose (DD) of 1.8 Gy up to total dose (TD) 54 Gy, and simultaneously in the ventricles (CTVventr) with DD 1.6 Gy up to TD 48 Gy.

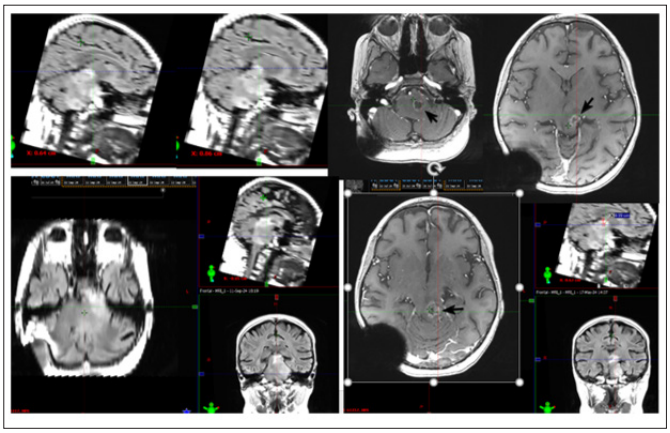

Figure 4: MRI/11.09.24 - MP reduction data in the size of the tumor engaging the brain stem. Structural changes and non -homogeneous contrasting are associated with a postradiation tumor necrosis. / Black arrows show tumor necrosis.

Discussion

DIPG is a high-grade glioma (HGG) that originates in the pons and is seen almost exclusively in children with a median age of diagnosis of 6–7 y [5-7]. However the infratentorial high-grade glioma, especially the intrinsic pontine glioma, remains one of the most treatment-resistant tumors, with an ultimate prognosis similar to adults with glioblastoma multiforme (GBM) [2]. Together with recent advances in molecular profiling, DIPG has been classified as a new pathologic entity called "diffuse midline glioma, H3K27M-altered" by the World Health Organization Without any treatment, the prognosis is very dismal with a median survival of approximately 4 months [8-11]. The POG 92-39, a phase III prospective randomized controlled trial, comparing hyperfractionated (1.17 Gy/fraction twice daily up to 70.2 Gy) and conventional (1.8 Gy/fraction once daily up to 54 Gy) radiotherapy with cisplatin showed no improvement with either approach in progression or survival Considering the paucity of data in favor of hyperfractionation radiotherapy, hyperfractionation radiotherapy is not promising in clinical practice and undesirable because of the discomfort of two sessions per day and possible damage to the healthy organs caused by higher doses [4-12].

The phase III non-inferiority randomized trial comparing hypofractionated (39 Gy in 13 fractions and 45 Gy in 15 fractions) and conventional fractionated (54 Gy in 30 fractions) radiotherapy was performed and recently published [13]. Other retrospective studies published usually used a reirradiation regimen of 18–20 Gy in 10 fractions and reported a median OS of 3–7 months after re-irradiation with an acceptable tolerability [14,15]. Most clinical trials recommended a 1–2-cm margin in addition to the gross tumor volume (GTV) for the clinical target volume (CTV) [16,17]. Recent advances in molecular profiling has ushered in a new era of DIPG, leading to the development of new targeted approaches to treat DIPG [4].

Temozolomide (TMZ) is an orally administered methylating agent that has shown promising responses in a subset of adults with recurrent or newly diagnosed high-grade glioma [18-22]. The addition of temozolomide to RT for newly diagnosed adult glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. Two-year survival again favored the combination of TMZ plus RT (26% vs 10% for RT alone) [23].The phase II study was performed to determine the safety, tolerability, and efficacy of concomitant radiation plus temozolomide therapy followed by adjuvant temozolomide therapy in patients with newly d

iagnosed GBM. During the concomitant treatment phase, grade 3 or 4 neutropenia, thrombocytopenia, or both were observed in 6% of patients, including two severe infections with Pneumocystis carinii [22]. The most significant benefit with TMZ is gained from its activity as a radiosensitizer and further suggesting that even low doses have clinically significant activity with lower rates of toxicity [24]. The inclusion of TMZ to re-irradiation has been wellstudied and shown to be safe and effective with median survival ranging from 5.1 to 10.1 months after combination therapy [25,26]. The concomitant chemoradiotherapy followed by adjuvant chemotherapy may prolong the survival of patients with glioblastoma [22]. Direct infusion of the therapeutic agent into the tumor bed via convection-enhanced delivery (CED) is another approach that is now gaining momentum. CED uses a stereotactically placed catheter with attached pump to provide positive pressure and maintain convective flow, bypassing the blood–brain barrier and providing direct localized drug delivery into the tumor [27].

Cohen et al. presented a summary of 61 patients treated with concurrent temozolomide and radiotherapy, followed by adjuvant temozolomide with 1-year OS rate of only 39%. Another study using a combination of temozolomide and cis-retinoic acid with radiotherapy in children with diffuse intrinsic pontine glioma (DIPG) estimates that, because of the favorable response rates after the completion of concurrent radiotherapy with TMZ along with the tendency toward longer OS and minimal toxicities and the small number of recruited patients, we suggest that this concurrent radiotherapy regimen and TMZ should be considered for further investigation in a larger series of patients rather than as a novel treatment strategy that should be adopted by all [28,29].

Combined with Temodal radiotherapy in pediatric brainstem gliomas reports that median survival of patients with primary disease volume less than 40cc is 26 months whereas when the volume is more than 40cc the median survival is 13.5 months. Their study reported a good median survival as compared to all other studies [30]. Distant leptomeningeal spread, while relatively rare in DIPG, has been documented in upwards of 20% of cases, and has raised the concern for complete neuraxis staging at diagnosis [31].

A randomized trial by Pediatric Oncology Group with concurrent chemotherapy and dose escalation also showed no significant benefit over conventional treatment [32]. In a study from Indian subcontinent Jalali et al., has shown a median survival of 9.15 months but this study did not show any improvement with the addition of temozolomide to radiotherapy [33]. In one of the pediatric studies, 2 of 5 children with recurrent high-grade astrocytoma and 1 of 10 children with diffuse brainstem glioma experienced objective responses to treatment [34]. Chemoradiotherapy with TMZ followed by adjuvant TMZ is not more effective than previously reported regimens for the treatment of children with DIPG [17]. A number of authors observe leptomeinteal spread in glioblastoma in adulthood, as well as in DIPG [35,36]. Our experience of hypofractionated and conventionally fractionated radiotherapy alone up to a total tumor dose of 54 Gy in three children with DIPG without histological verification showed tumor progression at 3, 6 and 12 months after its completion [37]. In one of the three clinical cases, despite re-irradiation due to tumor progression after 6 months from the initial hypofractionated RT, we observed leptomeningeal intraventricular spread (Figure 5). During ventricular irradiation, hydrocephalus occurred, causing exitus lethalis (Figure 6).

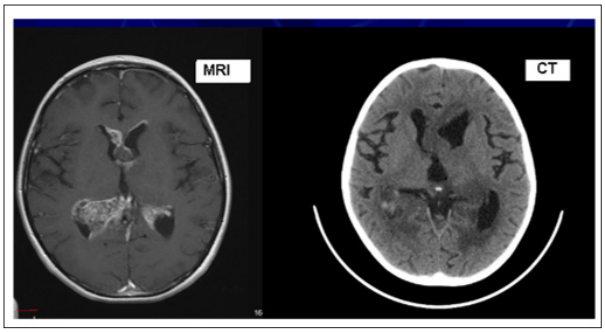

Figure 5: Intraventricular metastases after hypophractionated RT up to 50 Gy and conventional re-irradiation by another 20 Gy after 6 months due to tumor progression. A/ MRI data with Intraventricular metastases on the walls of brain ventricles with hyperintensity on T1+ GD and T2 FSE images. B/ CT findings of deformed ventricles

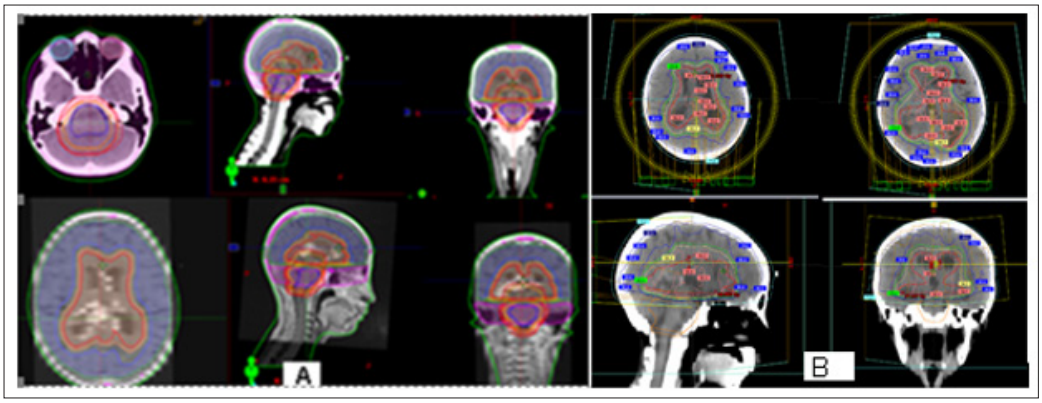

Figure 6A: Contouring and fusion of the three targeted volumes (both of the previous tumor irradiation) as a preparation for radiotherapy of supratentorial brain parenchyma with lateral ventricles; B / IMRT with DD 1.5 Gy up to TD 30Gy in the supratentorial brain parenchyma with simultaneus brain ventricles boost with DD 1,8 Gy up to TD36Gy.

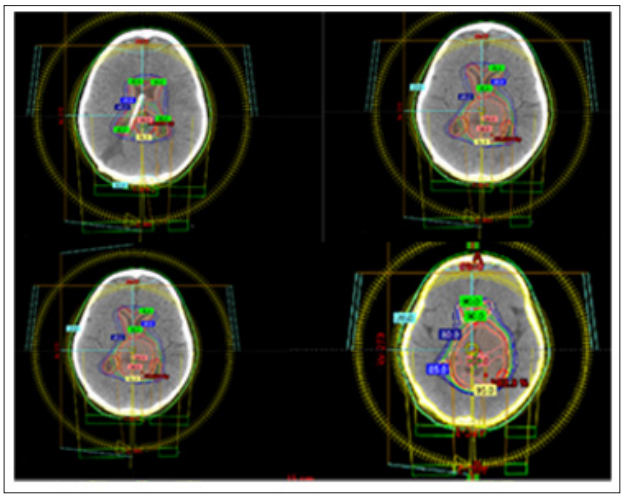

Figure 7: Intensity modulated radiotherapy (IMRT) according to the VMAT method in the tumor area (GTV) with coverage zone (CTVp) using 30 fractions with a daily dose (DD) of 1.8 Gy up to total dose (TD) 54 Gy, and simultaneously in the ventricles (CTVventr) with DD 1.6 Gy up to TD 48 Gy.

The following practice is necessary for patients with pontine-centered mass lesions thought not to be resectable is to proceed with diagnostic biopsy if the following two criteria are met: 1) there is diagnostic uncertainty based on symptomatology and/or imaging, and 2) stereotactic biopsy is felt to be safe based on multidisciplinary case review with neurosurgical evaluation [35].

Since in the presented clinical case stereotactic biopsy is high risk and imaging data suggest DIPG, our previous experience of tumor progression to or in the ventricles, was a prerequisite to expand the target volume to include the cerebral ventricles (Figure 7), as well as to conduct a combined with Temodal radiotherapy.

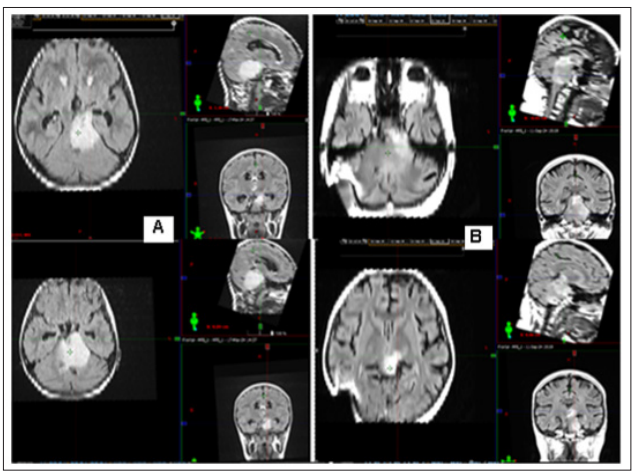

Figure 8: Comparison of MRI images a/ before combined with Temodal radiotherapy and in/ 2 months after the completion of the Temodal radiation treatment, followed by 2 separate courses of Temodal.

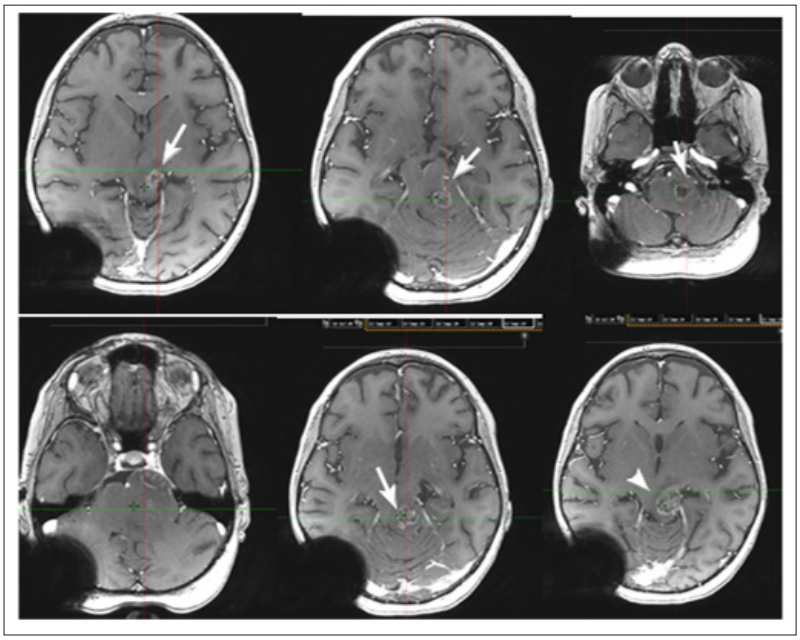

Figure 9: MRI image of the tumor necrosis 2 months after combined with Temodal radiotherapy, followed by 2 separate courses Temadal / white arrows show necrosis.

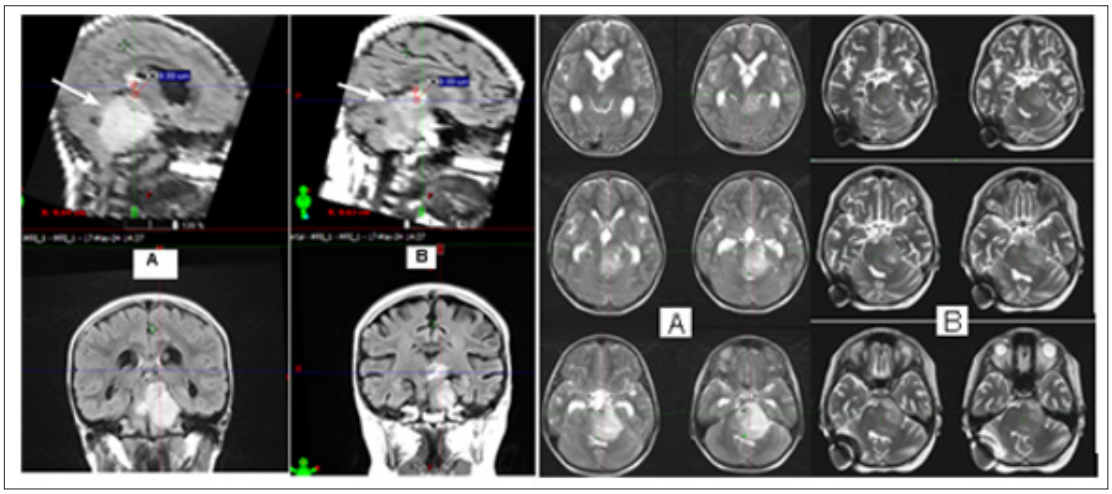

Figure 10: Comparison of MRI A/ before and B/ after combined with Temidal radiotherapy - MRI data on leptomeningeal pseudoprogression of the tumor on the left up to the ventricles by 0.5 cm.

For the first time in the Anglo-language medical literature, a MRI image is presented at DIPG, after combined with Temadal RT, which reports tumor necrosis in partial tumor reduction and leptomeningeal pseudoprogression (Figure 8, Figure 9, Figure 10).

Parenchymal pseudoprogression in brain tumor patients is well-documented, but worsening leptomeningeal enhancement following therapy may also represent treatment effects [38].

The likely explanation of the leptomeningeal pseudoprogression is radiation-induced disruption of the bloodbrain barrier in the region, resulting in leakage of contrast and leptomeningeal enhancement. Following radiotherapy, and usually within 2–3 months, some tumors may display radiographic worsening resulting from inflammation and necrosis in response to treatment, mimicking tumor progression [39].

Conclusion

DIPG is a high-grade glioma that originates in the pons and is seen almost exclusively in children. The conclusion due to the adverse prognosis with a 12- month survival is that conventional radiation to a total tumor dose 54 is standard. In order to increase the survival in this clinical case, we decided to conduct a simultaneous Temozolomide RT with an extended target volume with the inclusion of the ventricles. Two months after the Temozolomide IMRT, the MRI reported a tumor reduction with a distinguished tumor necrosis, which is evidence of the radio -sensitization effect of the Temozolomide.

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