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Re- Craniospinal Radiation Therapy of Subependimal Periventricular and Leptomeningeal Metastases in Adult Medulloblastoma- Clinical Case with Literature Overview

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Abstract

We present a 37 year old woman with medulloblastoma diagnosed 7 years ago. Subtotal tumour extirpation was carried out, followed by craniospinal radiation therapy (CSRT) with total dose (TD)-36 Gy and boost in cerebellum upto TD-54 Gy with daily dose (DD) 2 Gy in 27 fractions. After 4 years disease progression-free survival, three local relapses had been manifested (2017, 2018 and 2019), which have been surgically removed. Since the operation of the third relapse, 6 courses combined chemotherapy with Etoposide and Carboplatin have been conducted. In the background of the last chemotherapeutic course, MRI of the craniospinal axis visualizes diffuse subependimal periventricular metastases, combined with leptomeningeal metastases in the cerebellum and the entire spinal axis.

The re-CSRT with linear accelerator was conducted with the Volume Modulated Arc Therapy (VMAT) method in the spinal cord upto TD-24 Gy; cauda equina upto TD-28 Gy; in cerebellum upto TD-24 Gy; the two hemispheres upto TD-26 Gy and paraventricular upto TD-30 Gy with daily dose (DD) 1.8 Gy in 17 fractions. The summary biologically equivalent TD are consistent with the tolerant radiation doses of the spinal cord and the central brain structures. Three months after the completion of the re- CSRT we conducted an MRT of the brain and cervical spinal cord, which reported a lack of subependimal periventricular and leptomeningeal metastases in the brain, cerebellum and cervical spinal axis. For the first time in English medical literature a significant local effect on subependimal periventricular and leptomeningeal metastases after re-CSRT in medulloblastoma in adulthood was reported.

Keywords: Medulloblastoma in Adulthood, Leptomeningeal Disease, Subependimal Periventricular Metastases, Re-Craniospinal Radiotherapy

Abbreviations: CSRT: Craniospinal Radiation Therapy; TD: Total Dose; DD: Daily Dose; VMAT: Volume Modulated Arc Therapy; SC: Systemic Chemotherapy; BED: Biologically Equivalent Doses; MB: Meduloblastoma; LMD: Leptomeningeal Disease; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; RT: Radiotherapy; WBRT: Whole Brain Radiotherapy; CSI: Craniospinal Irradiation; FSRT: Focal Spine Radiotherapy; ITC: Intrathecal Chemotherapy; BSC: Best Supportive Care

Introduction

Meduloblastoma is a rare disease in adolescents and young adults, diagnosed in 1% of all brain tumours [1,2]. Medulloblastoma behaves differently in adults than in children, and is identified as a different biological and clinical entity. The prognosis and survival directly depend on the volume of the surgery, the magnitude of the postoperative brain residue (> 1.5 cm2), the infiltration of the IV ventricle, the metastatic disease, the adjuvant chemotherapy, the histological subtype and the tumour localization [1,3-5]. Subtotal surgical resection and evidence of disease dissemination are considered poor prognostic factors [6]. In adult patients, the five-year progression-free survival rate ranges from 45% to 78% depending on the risk class [7-9]. Re-irradiation is frequently undertaken for isolated brain relapses. A meta-analysis of brain re-irradiation found no cases of necrosis if the total dose (TD) was lower than 100Gy (2 Gy daily fraction dose; $\alpha:\beta = 2$ Gy) [2]. We present the first published case with leptomeningeal medulloblastoma disease in adulthood after 7 years of initial diagnosis and treatment, in which we conducted a re-CSRT.

Clinical Case

We present a 37 year old woman with medulloblastoma diagnosed 7 years ago. Subtotal tumour extirpation was carried out, followed by craniospinal radiation therapy (CSRT) with TD-36 Gy and boost in cerebellum upto TD-54 Gy with daily dose (DD)

2 Gy in 27 fractions. After 4 years disease progression-free survival, three local relapses had been manifested (2017, 2018 and 2019), which have been surgically removed. Since the operation of the third relapse, 6 courses combined systemic chemotherapy (SC) had been conducted by regimen: first day Carboplatin 300mg/m2 and from the first day until the third day Etoposide 100mg/m2, with a one-month interval. After the 4th SC course, due to anemia and thrombocytopenia, 2 days treatment had been applied with Methylprednisolone 40 mg/daily, Vit.C 2x5ml./daily and Ca Gluconici 2x10ml//daily, followed by hemotransfusion. With a good blood count, 2 more courses SC on the same regimen, were continued. In the background of the last chemotherapeutic course, MRI of the craniospinal axis visualizes diffuse subependimal periventriculare metastases, combined with leptomeningeal metastases in the cerebellum and the entire spinal axis (Figures 1 & 2).

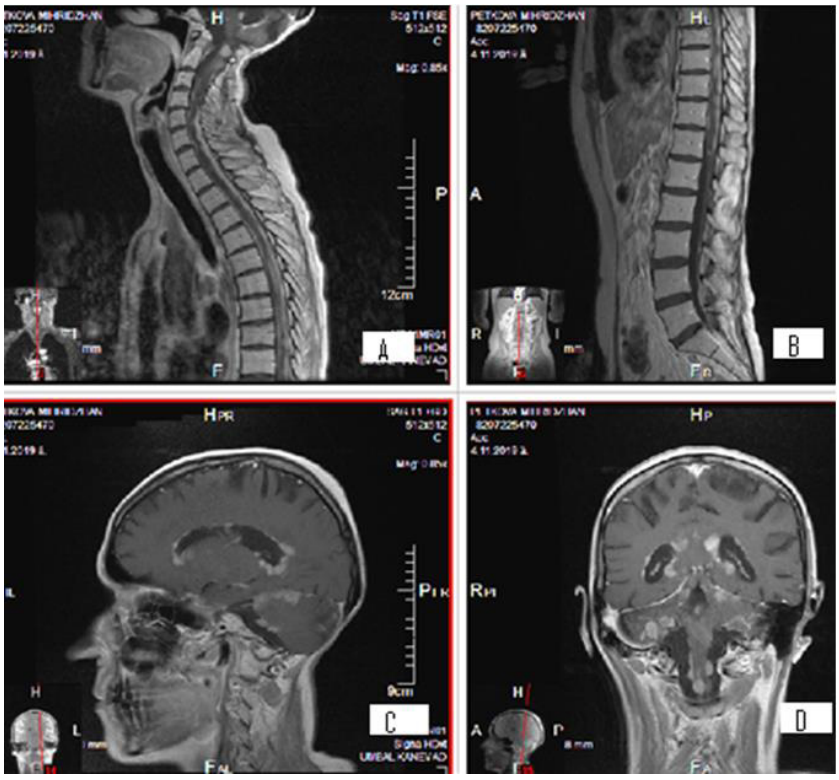

Figure 1: A, B/ SAG T1 FLAIR MR postcontrast images showing hyperintense leptomeningeal spinal lesions; C, D/ SAG T1 FLAIR MRI and C/COR T1 FLAIR MRI-postcontrast images showing hyperintense nodular subependymal and leptomeningeal brain lesions, predominantly infratentorial, with coverage of the cerebellum and medulla oblongata

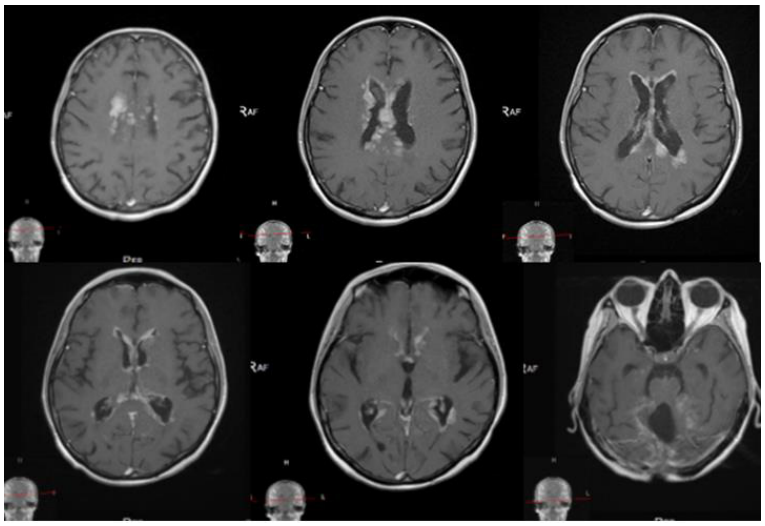

Figure 2: AX T1 FLAIR MR postcontrast images showing hyperintense subependymal periventricular and leptomeningeal brain lesions in triple local relapsed medulloblastoma

The re-CSRT with linear accelerator was conducted with the Volume Modulated Arc Therapy (VMAT) method in the spinal cord upto TD-24 Gy; cauda equina upto TD-28 Gy; in cerebellum upto TD-24 Gy; the two hemispheres upto TD-26 Gy and paraventricular upto TD-30 Gy with DD-1.8 Gy/17 fractions (Figure 3). The summary biologically equivalent doses (BED) are consistent with the tolerant radiation doses of the spinal cord and the central brain structures (Table 1).

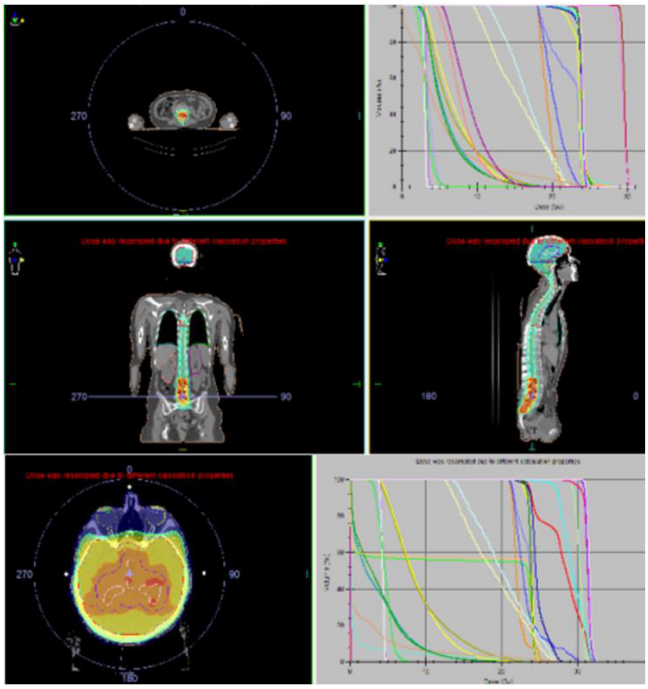

Figure 3: The re-CSRT with linear accelerator was conducted with the VMAT method in the spinal cord upto TD-24 Gy; cauda equina upto TD-28 Gy; in cerebellum upto TD-24 Gy; the two hemispheres upto TD-26 Gy and paraventricular upto TD-30 Gy with DD-1.8 Gy/17 fractions

Target	D1 Gy	70% D1 Gy (after 7 years)	α/β Gy	D2 Gy	BED2 Gy	Total BED Gy
Cerebellum	54	37.8	3.3	24	23.1	60.9
Brain	36	25.2	3.3	26	25	50.2
Paraventricular	36	25.2	2	30	28.9	54.1
Spinal cord	36	25.2	2	24	22.8	48
Cauda equina	36	25.2	4	28	27.1	52.3

D1- total dose of the first CSRT; Gy- a unit for measuring a realized dose; D2- total dose of the second CSRT; α/β- ratio of two constants-linear and exponential in Gy

Table 1: Summary biologically equivalent dose (BED) after the first and second CSRT in the separate areas of the brain and spinal axis

The prescribed doses to targets are realized in 1 basic and four bias dosimetry VMAT plans using two isocenters and one adjacent gap between targets.

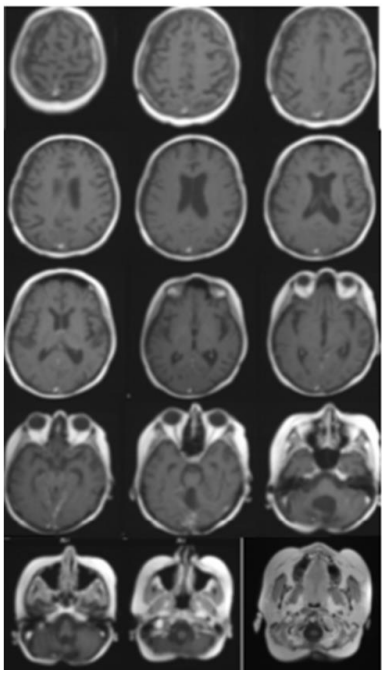

Figure 4: AX T1 FLAIR MR postcontrast images without subependymal and leptomeningeal brain lesions, three months after the re-CSRT

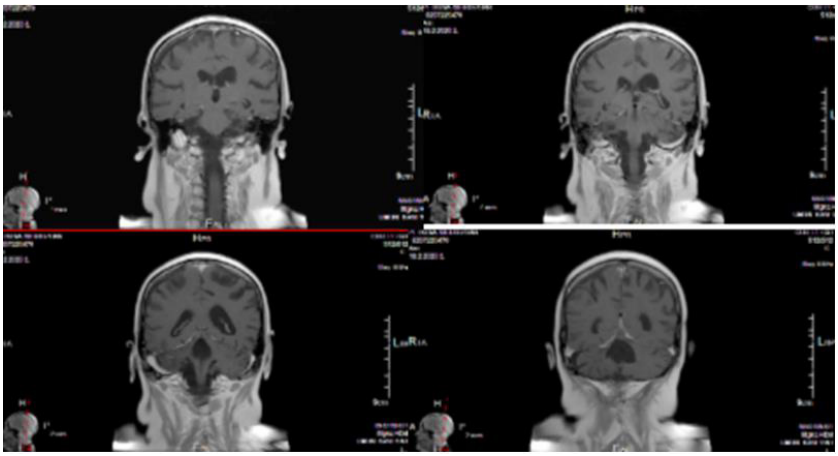

Figure 5: COR T1 FLAIR MR postcontrast images without subependymal and leptomeningeal brain lesions, three months after the re-CSRT

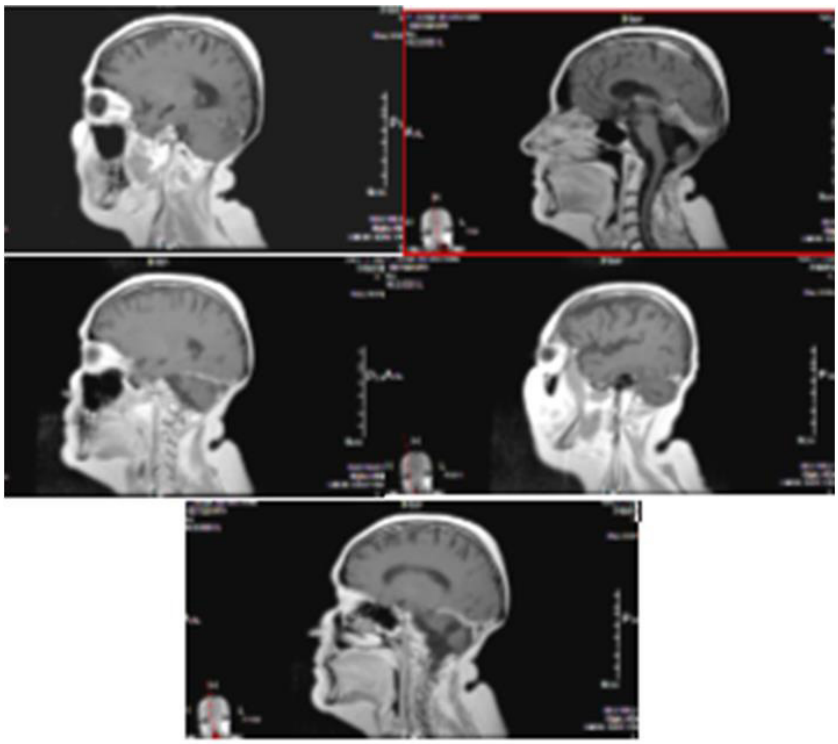

Figure 6: SAG T1 FLAIR MR postcontrast images without subependymal and leptomeningeal brain lesions, three months after the re-CSRT

In the first phase of irradiation two Volume Modulated Arc Therapy (VMAT) plans with 2 double arcs with different collimator degrees each were used and in the second phase three VMAT plans with one or two double arcs with different collimator degrees were used. Three months after the completion of the re-CSRT, we conducted an MRT of the brain and cervical spinal cord, which reported a lack of subependimal periventrikular and leptomeningial metastases in the brain, cerebellum and cervical spinal axis (Figures 4-6).

Discussion

Meduloblastoma (MB) is a malignant embryonal tumour, a subtype of primitive neuroectodermal brain tumors (PNET), predominantly growing infratentorally in the cerebellum [10]. The annual new incidence of MB in teenage and adulthood was only 0.05 to 100 000 [11]. Late relapse is common in adult medulloblastoma, and the overall survival of relapsed patients usually ranges from 12 to 15 months. Treatment at recurrence is still debated and after reoperation includes stereotactic or normofractionated radiotherapy, and high-dose chemotherapy with autologous bone marrow transplantation [2]. In the presented patient were performed 3 reoperations of local relapses in the cerebellum, and only after the third reoperation systemic chemotherapy (SC) was performed. After six courses of SC subependimal periventricular and leptomeningeal metastases were established, which was the reason to re-CSRT (Figure 3). The summary BED are consistent with the tolerant radiation doses of the spinal cord and the central brain structures. In humans, there is evidence that the risk of myelopathy is low at radiation doses upto a median cumulative BED 135Gy ($\alpha:\beta$ = 2 Gy for cervical and thoracic cord and 4 Gy for lumbar cord), when the time interval between re-irradiation

is not shorter than six months and the dose for each course is <98Gy BED [12]. Data exist concerning the re-irradiation of brain tumors to a median cumulative BED2 (biological equivalent dose in 2Gy fractions) of 200Gy, with at least one year between the two treatments; long-term complications related to the retreatment were seen in patients with a BED2>204Gy (α:β = 2 Gy) [13].

Leptomeningeal disease (LMD), also known as leptomeningeal carcinomatosis, is a rare cancer complication in which malignant cells infiltrate the layers of the central nervous system (CNS), known as meninges, and lead to significant morbidity and mortality [14]. Today, it is known that this condition occurs in ~5% of all cancer patients, presenting most commonly in primary diagnoses of breast cancer (41%), lung cancer (24%), gastrointestinal tract malignancies (13%), and melanoma (12%) [15-17]. The anatomy of the neuroaxis consists of the brain and spinal cord, covered by the meninges, which are comprised of dura mater, arachnoid membrane, and pia mater. The leptomeninges refers to the two most inner layers, arachnoid membrane and pia matter, including the subarachnoid space, which separates these two sheets, and is the location of the cerebrospinal fluid (CSF). The CSF is the location of circulating tumor cells in patients with LMD. The pathogenesis of LMD is multifaceted, and can include direct extension from pre-existing CNS tumors or systemic tumors that follow peripheral nerves into the subarachnoid space, as well as infiltration through hematogenous dissemination, or even seeding of the subarachnoid space during surgical procedures [16,18-21].

Subependimal and Leptomeningeal Metastases in Meduloblastoma

Of particular interest in the presented clinical case are rarely observed diffuse subependimal periventricular meduloblastoma metastases, combined with leptomeningeal in the cerebellum and spinal cord. In English literature we found similar subependimal periventricular metastases in solid systemic tumours such as small cell lung cancer [22,23] and cerebral glioblastoma [24]. Almost all clinically significant metastases from the medulloblastoma are located in the leptomeningeal area, clinging to the soft brain sheath under the arachnoid membrane and are poured from the cerebrospinal fluid [10]. The metastasis model is limited to leptomeningeal space, based on assumptions and poorly maintained empirical evidence that MB spread by direct distribution in the cerebrospinal fluid of tumor cells of the primary MB. Subsequently, tumor cells are implanted and grow on the surface of the soft brain matter [25]. By the presence of circulating in the blood meduloblastoma tumor cells in an untreated patient, it is proved that MB can spread by hematogenous way to the leptomeningeal space and form leptomeningeal metastases [10]. This hematogenous dissemination also applies to the choroidal plexus, localized in the entire ventricular system of the brain, given the relatively high cerebral inflow of blood (5 times higher than that in the brain parenchyma) and the porous endothelium of its capillaries [26,27].

Multimodal Treatment in LMD

Standard treatments for LMD include neuroaxis directed therapies in addition to optimal systemic therapy for the primary and extra-CNS disease. Radiotherapy (RT) is commonly used either focally to treat symptomatic sites and areas of bulky disease that will be unlikely to be adequately treated with chemotherapy or in some settings to treat the entire neuroaxis [14]. Regardless of systemic and local control of the primary disease, prognosis in the setting of LMD is very poor, with reported average survivals of ~2–4 months, even with treatment [28-31]. A meta-analysis of LMD survival in adulthood with primary brain tumours following different types of treatments was performed - whole brain radiotherapy (WBRT), craniospinal irradiation (CSI), focal brain RT (FBRT; fractionated or stereotactic radiosurgery (SRS), focal spine radiotherapy (FSRT), intrathecal chemotherapy (ITC), intraventricular radioisotope, systemic chemotherapy (SC), and best supportive care (BSC). The median OS from the diagnosis of LMD ranged from 2.8 to 10.2 months. These studies indicated that patients treated with a combination of SC+RT had significantly prolonged survival compared to either therapy alone or BSC.

In the presented clinical case, the patient was designated for BSC, but given the young age and the relatively good general condition, we considered that re-CSRT was the last curative strategy, that should help. After a strict determination of biological equivalent additional doses in the brain structures and spinal cord, we performed the re-CSRT. In general, in the case with CSRT, due to irradiation of many bony structures (skull, spine and pelvic bones) thrombocytopenia manifests, which is treated with Dexamethasone (2 or 3 times 8 mg. /daily), Methylprednisolone 40 mg. /daily and Ecomer (3 times 2 caps./ daily). If necessary, hemotransfusion of thrombocytic mass is carried out. The patient suffered a good re-CSRT with mild thrombocytopenia (80.0 109/l) at the end of the radiotherapy. Three months after the completion of the re-irradiation, we conducted an MRT of the brain and cervical spinal cord, which reported a lack of subependimal periventricular and leptomeningial metastases in the brain, cerebellum and cervical spinal axis (Figures 4-6). The patient was directed to continue treatment with SC.

Conclusion

Meduloblastoma in adulthood is a rare oncological disease. Leptomeningeal disease is a rare cancer complication in which malignant cells infiltrate the layers of the central nervous system. Regardless of systemic and local control of the primary disease, prognosis in the setting of LMD is very poor. There is limited high-quality evidence to guide the optimal use of radiotherapy and re-irradiation for the treatment of LMD in adulthood meduloblastoma. Advances in radiotherapy planning and delivery techniques now make possible the achievement of better target definition and highly conformal treatments. Retreatment with CSRT of LMD in meduloblastoma reaches total local control of the metastatic subependimal periventricular and leptomeningeal cells. This is evidence of the expressed radiation sensitivity of the metastatic meduloblastoma cells. Despite the aggressive regimen of re-CSRT, covering an extensive CTV, including the CNS, spinal cord and a large volume of bone-marrow structures, radiation therapy is well tolerated against the background of dexamethasone (2 or 3 times 8 mg. /daily) and Ecomer caps. (3 times 2 caps./ daily) throughout the radiotherapeutic course [11].

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