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Case Report and Literature Review of Spinal Glioblastoma Multiforme in Childhood

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Abstract

We report a case of a 15 year old girl, with weakness on the lower extremities and sensory loss especially on the right side. MRI showed an intramedullary intraspinal mass at thoracic to lumbar spine level (T10-L1). A partial resection was performed and the result of Hystopathologic was Glioblastoma multiforme (GBM) WHO grade IV. She received adjuvant chemotherapy and craniospinal irradiation.

Keywords : Spinal cord Glioblastoma, spinal tumor, children, temozolomide, radiotherapy

Introduction

Glioblastoma multiforme (GBM) is a glial neoplasms (WHO classification grad e IV) and the most common primary malignancy of the central nervous system (CNS).[1] It also has poor prognosis and survival rate.[2] The incidence of spinal tumors with a high grade malignancy (WHO classification grade IV) is rare, accounting for less than 1% of CNS tumor in children and adolescents worldwide.[3] Most cases are found in young adult patients, and cervical spine is the most common location.[4] Thoracic region and conus medullary also the predilection site of the GBM, approximately 7.5% of all intramedullary gliomas is a GBM tumor .[5]

The purpose of this paper is to study spinal GBM from the perspective of epidemiology, diagnostics, and management, especially in the field of radiation oncology. Poor prognosis and survival rate is a challenge for all clinicians in providing the best and maximum possible therapy to control and prolong patient life expectancy, especially in young patients as in the case illustration. We report the case of a 15-year old girl affected by a spinal GBM who had a extramedullary drop metastasis.

Case Report

A 15-year old girl, was referred from Pediatric Neurology with weakness on both of the lower extremities and sensory loss especially on the right side. On March 2014, she complained about weakness in both lower extremities and the family performed MRI in Penang, Malaysia, showed an intramedullary intraspinal mass at thoracic to lumbar spine level (T10 to L1). A partial resection surgery was performed in Penang. After the surgery the motoric strength increased. Pathological anatomy biopsi showed a glial tumor with suspicion of neuroblastoma. Patients were advised to continue treatment at pediatric oncology.

On May 15, 2014, the patient was brought to another hospital in Singapore with a decreased motoric condition of both extremities, right limb was 1/5 and the left was 4/5. And sensory loss on the right lower extremity. The pathologycal anatomy slides were re-reviewed with a final report of Glioblastoma multiforme (GBM) WHO grade IV. She asked for radiation treatment and chemotherapy to be continued at Surabaya, Indonesia.

Since June 2014, patient was treated in RSUD Dr. Soetomo Hospital Surabaya, Indonesia with chief complaint of numbness sensations, weakness in the lower limbs and defecation problems. Another whole spine MRI was taken on June 6, 2014, and showed an intramedullary mass extend at T9 to T12 level. Enhancing epidural focus below the mass and on the cauda equina showed suspicion of drop metastasis and leptomeningeal focus in the posterior cranial fossa also present of metastatic deposit. There was no abnormality in the brain MRI.

On July 2014, a spinal MRI showed extramedullary drop metastatic at C4 to L2, cauda equina and syringohydromyelia at T5. There was no abnormality in the brain.

For the treatment of GBM, she received two cycles of Temozolomide and Craniospinal irradiation. The dose was given at 30.6 Gy in 17 fractions, 1.8 Gy per fraction. On September 2014, post chemotherapy and irradiation MRI showed a good response of therapy, with a residual mass at Vertebra Thoracal 4 - Vertebra Lumbal 1 .

The results of the MRI examination on September 17th 2014, showed a good response with a

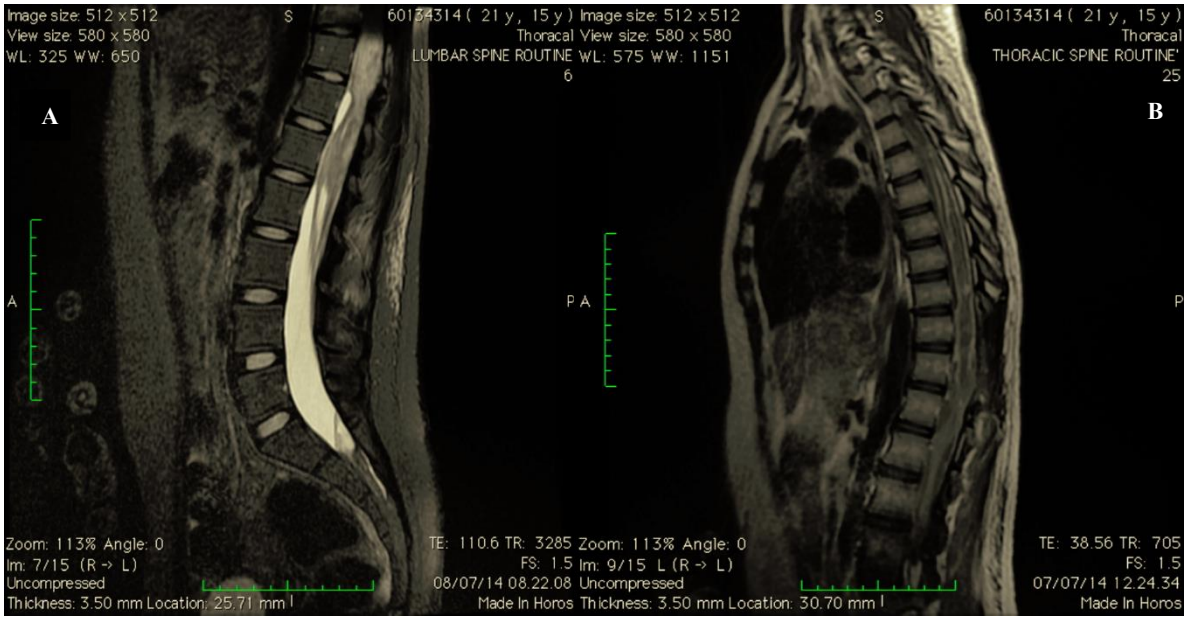

Figure 1. A and B: Magnetic Resonance Imaging (MRI) : Sagittal T2-weighted MRI, which show drop metastatic extramedullary from C4 to L2 and syringohydromyelia at T5.

residual mass as high as VTh 4 – VL 1 but the mass appeared to be reduced accompanied by lots of gliosis

as high as VTh 4 – VL 1 and Siringohydromyelia in the cervical was no longer visible.

On October 10th 2014, the patient complained that both lower limbs were still felt numbness, she also complain of pain in the right elbow. Then the patient was planned for a tumor bed radiation booster, with a dose of 16 x 1.8 Gy.

On December 2014, the patient was still unable to walk.

On February 11st 2015, both legs were able to move, then the patient was scheduled for another MRI and the results showed that almost all of the tumors were recurrent as areas of gliosis and intra-medullary syringohydromyelia as high as VC 4 - 5. The patient was planned to do physiotherapy, the leg cannot be moved but if she is lying, the right leg can be moved.

On July 7th 2015 the patient complained of dizziness and repeated MRI with the result that there were no intraaxial or extraaxial masses and found no abnormalities.

On September 1st 2015, the patient's condition began to weaken, there was inferior paraplegia. The patient performs alternative medicine with acupuncture.

On January 19th 2016, the patient complained of an injury to the back of the waist and found a decubitus wound, and the patient underwent another MRI and obtained intramedullary residual glioblastoma as high as VC 6 – VTh 10 level accompanied by bulging of the spinal cord pro evaluation post chemotherapy and visible radiation enlarged, Syringohidromyelia as high as VC 5 to the medulla oblongata seemed to increase in size, and no recurrent mass was seen in the cervical region. The mass appears to be reduced with a lot of gliosis, siringhydromyelia in the cervical is not visible. Another spinal MRI on March 2015 showed that almost all of the tumor residues had become gliosis.

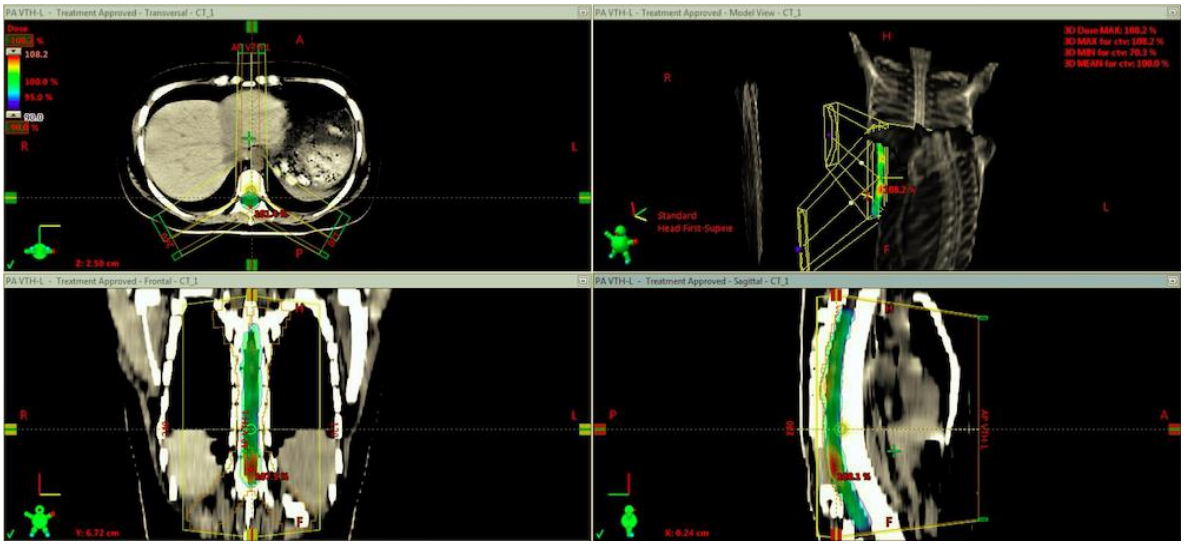

Figure 2. Isodose distribution and target volume of spinal irradiation.

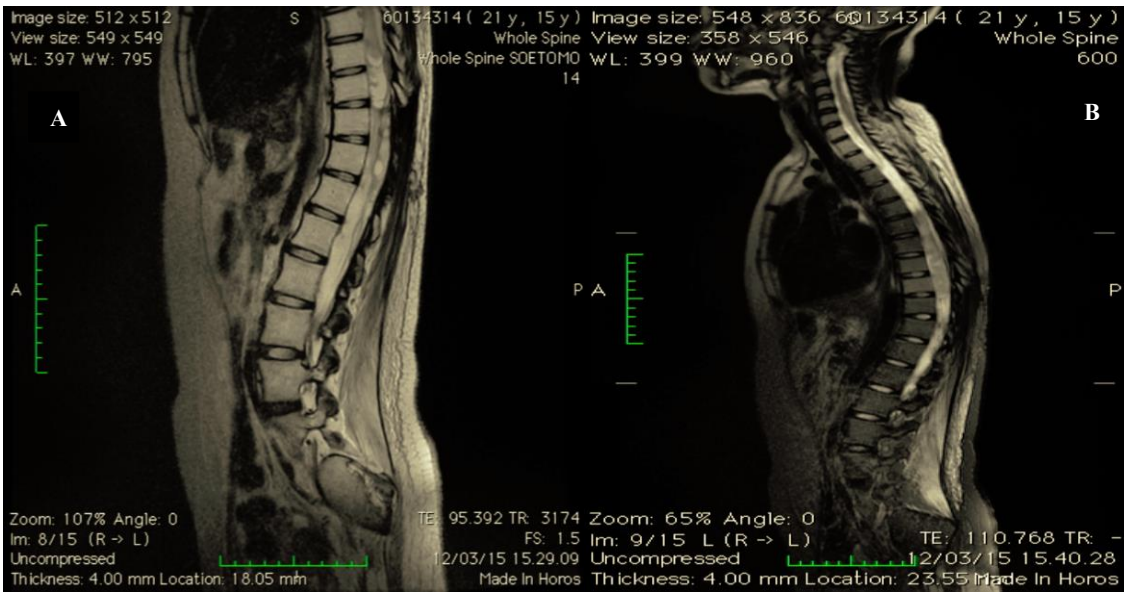

Figure 3. A and B : Magnetic Resonance Imaging (MRI) : Sagittal T2-weighted MRI, showed intramedullar residuall mass from T4 to T10 with gliosis area, and syringohydromyelia at C4-5

Syringohydromyelia on intramedular as high as Vertebra Cervical 4-5 level.

Discussion

Glioblastoma multiforme (GBM) is a glial neoplasms and the most common primary malignancy of the central nervous system (CNS).[1] The incidence of spinal tumors with a malignancy is rare, accounting for less than 1% of CNS tumors in children and adolescents.[3]

In a study of 872 children with spinal tumors, 36% were intramedullary tumors, 27% were intradural extramedullary tumors, while 24% with extradural tumors and the remaining 13% cannot be classified.[6] In children, 75%-90% of intramedullary tumors are astrocytoma with 85%-95% having low grade malignancy, fibrillar or pylocytic juvenile. Less than 10% of spinal astrocytomas in pediatric and 25% in adults are tumors with high grade of malignancy.[7] The incidence of GBM is more common in children over 12-year old, and the most common symptom was limb weakness, sensory disturbances, back pain, bladder and bowel disturbances.[8] According to this case, she complaint weakness in both lower limb and followed by sensory loss on the right side limb. Disease progression also tended to be rapid, consistent with a mean tumor doubling time of 39.5 days.

The analysis by Timmons, cervical spinal cord is the most common location of GBM (33%), tumors covering multiple areas of the spinal cord (30%), and then the thoracic region (29%) of the population.[2] Tumor located in cervical was 32%, thoracic 28.3%, cervicothoracic 18.9% and at a conus 18.9%.[8] In this case, mass is founded at Thoracal 10 to Lumbal 1 level. According to the survival rate, the age group 13–18 years old had worst survival than other age groups. [8]

MRI is a gold standard for diagnostic modality in d etecting spinal canal tumors and it can assessed the character of the cerebrospinal fluid. The use of gadolinium (Gd-DTPA) also increases the sensitivity in detecting leptomeningeal metastatic process. Therefore MRI is mandatory in patients with ependymoma or high grade malignant astrocytoma to exclude the possibility of seeding neuraxis or the presence of a primary intracranial tumor.[6] A whole spine MRI in this case showed enhanced of the epidural focus below the mass and in the cauda equina is suspicious for drop metastasis.

Histopathological examination to determine the type and nature (malignant or benign) of the tumor must be confirmed under any circumstances. Exceptions may be given in special circumstances, where emergency therapy is required to reduce spinal cord compression to the fullest concern of the patient. Histopathology shows nucleus atypia, cell pleomorphism, mitotic activity, vascular thrombosis, microvascular proliferation and necrosis.[9] Immunohistochemical assistance plays an important role. Based on the literature, it is said that GBM will provide a strong positive stain on both cerebral and spinal p53.[10] In addition, it also provides staining on GFAP (Glial Fibrillary Acidic Protein) and S 100 as well as high MIBI / Ki-67 proliferation index.[11]

Surgery procedure is the recommended therapy because it can preserved neurological status of the patient. The condition of infiltrative tumor is usually difficult to perform totally resection of the tumor.[7] During surgery, intraoperative neurophysiological monitoring is the standard therapy for intramedullary tumor resection. The monitoring depends on 2 main components: Somatosensory-Evoked Potentials (SEPs) and Motor Evoked Potentials (MEPs). The risk of postoperative paralysis is <1% in patients with no or minimal neurological deficits but is higher in patients who had substantial deficits before surgery.[6] The patient has received surgical therapy, but the resection cannot be maximized, this is probably because the tumor

margins are not clear. In accordance with the high degree of malignancy which usually has infiltrative properties and it is difficult to determine the boundaries of the tumor. For the tumor residues it is recommended to performed radiation and chemotherapy.

The role of chemotherapy is still not clearly defined because there are differences in therapeutic results, however chemotherapy is usually given to astrocytoma with a high risk of malignancy. Several studies have shown that chemotherapy can be given as either an adjuvant or primary therapy for tumor recurrence in children with high risk of malignancy.[7] Temozolomide is chemotherapeutic agent and the most common used therapy for GBM.[12] Kim *et.al* reported a study with 2 spinal GBM patients treated with concurrent radiation temozolomide followed by adjuvant temozolomide with a survival rate of 12 and 16 months.[6]

Research evidence suggests that adults who showed methylation of the Methylguanine-DNA Methyltransferase (MGMT) promoter have better outcomes with oral alkylating therapeutic agent such as temozolomide and are likely to have equal results as in children. Molecular factor analysis such as MGMT can help to guide therapy and as a predictor for treatment outcomes with combined radiation and chemotherapy.

In this case, chemotherapy has been given in 2 cycles with the Temozolomide regimen which has shown to provide good results for cerebral GBM. In addition, craniospinal radiation was also given considering that there was a metastatic drop and there was a possibility for intracerebral spread. The radiation dose was adjusted according to the condition of the patient, which was evaluated at 17 x 1.8 Gy with the possibility of increasing the radiation dose if possible. Postoperative adjuvant radiation is recommended for high risk malignancy because progressivity in spinal tumor can lead to worse neurological status condition. The radiation dose given is adjusted based on experience with cerebral tumors with high malignancy taking into account side effects according to QUANTEC study.[7] A small-scale study demonstrated prolonge d survival in patients with high-grade malignant tumors treated with craniospinal irradiation.[7] Craniospinal irradiation is usually not a routine indication of spinal tumors because tumor recurrence is usually lo cal. Nonetheless, diffuse neuraxis is frequently seen in patients with anaplastic ependymoma, malignant astrocytoma and myxopapillary ependymoma. Craniospinal irradiation can be considered in these circumstances.[6]

Tumors with high spinal malignancy, especially GBM, are associated with a high leptomeningeal spread, up to 58% in several series and as much as 47% in the cohort study conducted in St. Petersburg. Jude Children's Research Hospital.[3] The number of spreads is higher in spinal tumors with high malignancy than in brain tumors with the same histopathology. These events were associated with the anatomical location of the spinal tumor closer to the subarachnoid cavity than to the intracranial portion.[3] Intracranial dissemination in the course of spinal GBM accounts for 9 of 15 cases (60%). The exact mechanism of aggressive spread is not fully understood, direct spread to adjacent areas and via cerebrospinal fluid is the most likely explanation.[13]

Patients with proven leptomeningeal spread are candidates for craniospinal irradiation, but it is not clear the role of prophylactic craniospinal to treat extensive tumor volume without radiographic evidence of such spread. A journal states that adjuvant radiation in the form of prophylactic focal and cranial radiation due to the high rate of dissemination of leptomeningeal and cerebrospinal fluid causes mortality.[14] Current imaging techniques for evaluation of disease spread before radiation can also lead to inaccurate estimates of the actual extension of disease. The most appropriate condition is the dose and volume of radiation given is based on the consideration that is adjusted for each patient.[3]

At high degrees of malignancy, the Clinical Target Volume (CTV) limit for local radiation should be given a wider 1.5 cm. If there is cauda equine involvement, CTV should cover the entire thecal sac with volume widened over the sacroiliac joint. Failure to cover the entire thecal sac is associated with increased treatment failure.[6] In patients with highly malignant spinal tumors with evidence of dissemination in the cerebrospinal tract, craniospinal radiation (CSI) is given at a dose of 36-45 Gy with a booster to the local tumor up to 50.4-54 Gy at a dose of 1.8 Gy / fraction.[6]

In the current therapeutic protocol, adult patients with high malignant gliomas receive a dose of 54 to 60 Gy for local tumor + peritumoral to limit tumor infiltration of 1.8-2 Gy / fraction. The spinal cord is less tolerant of radiation so the dose is limited to 50 Gy to prevent myelitis. However, when used in conjunction with chemotherapy or radiosensitizers such as Temozolomide, consideration is given to a lower radiation dose. From the results of the study, a surgical post radiation dose > 35 Gy was shown to improve survival compared to smaller doses or not at all. Given the wide range of radiation doses, with different clinical considerations it makes more sense if the radiation dose is given according to each individual.[15]

Cranial field : simulated lateral opposing field, the inferior border is the cervical vertebrae as much as possible in the appropriate position also protects the oral cavity, neck outside the spinal canal, nasopharynx. For spinal field : one or 2 spinal field. The superior border begins at the inferior border of the cranial field, with the inferior border at S2. Width between 4-6 cm.[16] Conventional external radiation dose 50 Gy, 60 Gy and 60 Gy with fraction size 1.8-2 Gy / day, were associated with 0%, 6% and 50% incidence rates of myelopathy.

Pediatric patients and patients with chemotherapy may have decreased dose tolerance in the spinal cord, with reports of myelopathy occurring at

doses of 50 Gy or less. The radiated spinal cord may recover. Experiments on monkeys showed 76%, 85% and 100% recovery at 1,2 and 3 years after radiation. In humans, reirradiation was performed at least 6 months after the first radiation, and no myelopathy was found when the cumulative dose of EQD2 was not more than 60 Gy.[6]

Conclusion

1. Spinal GBM in children is rare and has a poor prognosis.
2. The best therapy is multimodality, with maximum possible surgical therapy followed by radiation and / or chemotherapy.
3. The role of chemotherapy regimens is the use of temozolomide, the optimal time for giving radiation or chemotherapy has not yet obtained definite results.
4. Radiation doses can be safely administered to neuraxis by limiting the dose tolerance of the spinal cord. The optimal therapy of surgery, radiation, chemotherapy and targeted therapy are needed although the rarity of cases makes prospective evaluation difficult to undertake.
5. The age, clinical condition and therapy that patients have had is highly variable. Similarly, radiation doses are associated with survival. Therefore it is stated that the radiation dose will be very different depending on each individual (individualized).
6. Spinal GBM is also more prone to leptomeningeal metastases and the whole spinal irradiation will better improve the survival.

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