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Case Report

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ADULT MEDULLOBLASTOMA RECURRENCE: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Medulloblastoma is a malignant embryonal tumor that commonly arises in the cerebellum. While it is the most common central nervous system malignancy in children, it is significantly less common among adults. Although surgery and radiotherapy are considered as therapeutic standards of medulloblastoma, addition of adjuvant chemotherapy is controversial. In a palliative situation, the place of chemotherapy is constantly progressing. ***Case report:*** We present a case of a 34-year-old patient with cerebellar vermis medulloblastoma. The patient underwent a subtotal resection which was classified as non WNT classic histology. Due to the persistence of a large tumor residue, postoperative radiotherapy was added followed by adjuvant chemotherapy. Despite a well-conducted treatment, the patient presented with a local tumor recurrence for which he was indicated to receive palliative chemotherapy. ***Conclusion:*** Addition of adjuvant chemotherapy can lead to better outcomes in adult patients with medulloblastoma. The recurrence of medulloblastoma after postoperative radiotherapy and chemotherapy is not very common, and the decision of therapeutic choice can be elaborate given the limited data currently available.

INTRODUCTION

Medulloblastoma is a malignant embryonal tumor that commonly arises in the cerebellum.[1]

While it is the most common central nervous system malignancy in children comprising 15-20% of all pediatric brain tumors, it comprises only 0.4-1.0% of adult brain tumors.[2,3]

MB is located in the cerebellar hemispheres or vermis and exhibits a male predominance in the adult population. The majority of affected adults (~63%) are aged 20–40 years, whereas occurrence in individuals aged >50 years is exceedingly rare.[4]

The majority of patients with central nervous system malignancies show manifestation of increased intracranial pressure, which is best explained as the result of hydrocephalus.[5] Headache, nausea, and vomiting are frequently the most common presenting symptoms; however, in older children and adults, ataxia can also occur.[6]

The etiology of MB remains unclear in most patients, both children and adults.[7] however, it seems that various mechanisms leading to MB are different among the two groups.[8] In addition, it has been reported that MB in adults has certain clinical and pathological features which are distinct with the presentations in children.[9,10]

Low incidence of MB in adults gives us a narrow perspective about the disease nature. In addition, it also makes standard procedures for treating the tumor in adults very difficult to establish.

Previous studies on the treatment of MB have demonstrated the importance of surgical resection and postoperative radiotherapy. However, the role of chemotherapy in the treatment of MB in adults is less clear due to the rarity of the tumor in this age group. Nonetheless, recent studies have reported the potential efficacy in adults with MB.[11,12,13,14]

The aim of our study is to study the clinical characteristics of this rare disease, and to present the surgical difficulties encountered, and especially to share our experience and providing specific information of treatment at the stage disease recurrence.

We report the case of a 34-year-old patient with medulloblastoma of the cerebellar vermis who, after having undergone surgery followed by postoperative

radiotherapy and adjuvant chemotherapy, had unfortunately disease recurrence.

CASE REPORT

We report the case of a 34-year-old patient with a history of chronic smoking and cannabism for 8 years, still ongoing.

He came at the hospital of specialties of Rabat, Morocco, with headaches, vomiting, vertigo and balance disorders that had lasted for 6 months. A brain CT was carried out, followed by a cerebral MRI on June 2019 which objectified the presence of a cerebellar expansive tumoral mass of the vermis involving the right cerebellar hemisphere, isodense - isointense with heterogeneous contrast enhancement, pushing back the 4th ventricle, inducing hydrocephalus.

The patient was then hospitalized in the neurosurgery department, where he underwent brain surgery on July 2019. Complete resection of the tumor couldn't be performed due to the heavy bleeding, resection was then incomplete. The surgical specimen was examined and the pathological reading concluded with the diagnosis of non WNT classic medulloblastoma. He also received an external ventricular bypass to manage the hydrocephalus.

The patient presented postoperative complication: infectious meningitis treated with antibiotics with a good clinical course.

Postoperative brain scan was performed on D 20 after the surgery objectifying vermis tumor residue measuring 23x18x17 mm surrounded by perilesional edema exerting a mass effect on the fourth ventricle.

A reoperation was attempted in February 2020 but was interrupted because of the bleeding and the drop in blood pressure; a 2nd attempt was made in April 2020 but was also unsuccessful, however the patient received a placement of ventriculoperitoneal shunt for management of hydrocephalus.

The patient was then lost to follow-up for 3 months, he remains asymptomatic until the onset of headaches and vertigo, he presented then to the department where he was operated on.

The patient was then referred to our Hospital "The National Institute of Oncology of Rabat", and was received in the radiotherapy department, the patient was in good general condition, he presented headaches, walking was possible without help but slightly ataxic.

A brain MRI was performed in July 2020 showing a large tumor residue in the posterior cerebral fossa, poorly defined, containing areas of necrosis, enhanced after injection of contrast product measuring 40x72x 42mm with no dissemination within or outside of the neuroaxis.

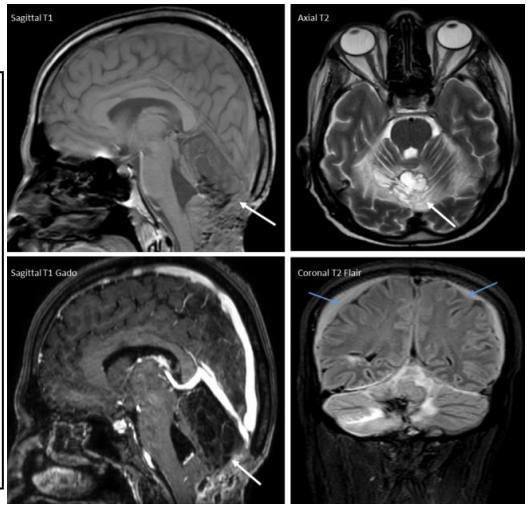

Fig. 1: MRI demonstrates a poorly circumscribed mass with heteregenous signal patterns within the vermis (white arrow). It is composed of mixed solid and cystic components with peritumoral edema.
The solid component demonstrates a patchy enhancement post contrast administration.
Punctuate intratumoral hypointensities represent focal calcifications.
As a result of the mass effect on the fourth ventricle, significant obstructive hydrocephalus has developed hence the placement of ventriculoperitoneal shunt). Note bilateral subdural hematomas after ventricular shunting (Blue arrow).

The decision of multidisciplinary consultation meeting was to carry out Radiotherapy followed by adjuvant chemotherapy. The patient then received Craniospinal Irradiation (CSI): 36 Gy with a boost of the the posterior fossa to 54Gy received in 5-6weeks without concomitant chemotherapy.

Irradiation had ended on September 17, 2020. Radiotherapy was followed by adjuvant chemotherapy with Etoposide cisplatin, a total of 6 cycles were administered from October2020 to February 2021 with good clinical tolerance and good therapeutic response.

Three months after the end of chemotherapy, the patient experienced worsening of symptoms including dizziness and trouble walking, a cerebral MRI was performed objectifying the progression of the disease with persistence of an irregular, multi-locular tumoral mass next to the operating site, measuring 61x32mm vs 40x72mm associated to perilesional edema. This mass infiltrates the meningeal relief, also appearance of new

lesions in the two cerebellar hemispheres. No bone signal abnormality or meningeal or epidural contrast enhancement was observed.

The staff decision of medical oncology department was to start palliative chemotherapy with TEMOZOLOMIDE at a dose of 200 mg / m² for 5 days, every 28 days.

Three cycles have been already administered since may 2021 with good tolerance of the treatment as well as an important clinical benefit.

DISCUSSION

MB is a malignant CNS tumor originating from the neuroepidermal layer of the cerebellum, first presented by Cushing and Bailey in 1925. This malignant tumor is the most common CNS tumor in children and is usually localized in the fourth ventricle, vermis or cerebellar hemispheres.

It has a peak incidence between 4 and 8 years of age, but it also occurs in adults with a peak incidence between 24 and 30 years of age. However, more than 85% of patients with MB are children younger than 15 years old.[15] Among adults, approximately 80% of MB patients are under 40 years of age, and cases in older adults (aged older than 60 years) are extremely rare. According to sex group, males have a higher incidence rate of MB than females.[16,17]

In adults, the tumor more frequently involves the cerebellar hemisphere; while it more frequently affects the vermis in the pediatric population.[5] however, the tumor in this was located in the cerebellar vermis.

MB commonly arises from the cerebellar vermis in the roof of fourth ventricle.[5]

The cell of origin from which MB derives has been controversial. Koeller and Rushing,[4] described undifferentiated cells in the posterior medullary vellum that are near the midline early in life, but exhibit lateral and superior migration with aging.

However, other studies suggested that the origin of MB is the restricted cerebellar granule neuron precursors.[18,19] They form a germinal center that develops in the rhombic lip located in the anterior part of the fourth ventricle, which later proliferate and migrate to become the external and internal granular cell layer in the cerebellum.[20] This theory of biological origin could explain the site of predilection on the dorsal surface of the cerebellar hemisphere in adults.

The WHO has described 4 histological subtypes: classic, large cell/anaplastic, desmoplastic-nodular, and medulloblastoma with extensive nodularity.[21]

More recently, Four molecular subgroups of MB have been identified (SHH, WNT; Group 3 and Group 4).[22] However, Remke et al. revealed that only 3 variants which predominantly exist in the adult population: SHH, WNT, and Group 4.[8] These molecular subgroups correlate with the clinicopathology, treatment options, and prognosis of MB.[23]

In this, we only know that he has a non WNT classic MB, we could not conduct more molecular investigation because other immunostaining techniques were not available and it would have cost more time and money if they were performed in another laboratory.

Based on these data, our patient might be classified as SHH or group 4 subtype, which is not correlated with good prognosis like in WNT subtype.

MB commonly presents with symptoms of increased intracranial pressure and cerebellar dysfunction evolving over a period of weeks to a few months. If the nuclei of the brainstem become damaged, the patients present with gait disturbance, diplopia and anesthesia. If the tumor involves the fourth ventricle, it may cause obstructive hydrocephalus.

Headache, nausea, vomiting, and blurred vision are the most common presenting manifestations. Funduscopic examination shows papilledema. As the disease progresses and the tumor infiltrates the brainstem, cranial nerves dysfunction becomes more common. Nystagmus and diplopia manifests as the results of cranial nerve IV or VI palsy. Ataxia is also commonly seen.

However, adult MB may have an insidious clinical course with slow progress, as in the case of our patient, who experienced symptoms for 6 months prior to presentation.

Sarkar et al.[24] reported in their study that the duration of symptoms in adults with MB was in the range 1–18 months (mean, 7 months), which seems to correlate with our patient's history.

The imaging characteristics of adult cerebellar MB are closely associated with the tentorium of the cerebellum or meninges which can cause diagnostic errors.

Computed tomography (CT) and MRI of MB is quite distinct between adults and children. In children, imaging of MB generally reveals solid, homogeneously enhancing, midline masses in the posterior fossa, while adult MB rarely gives this appearance , it present with poorly defined formation, less enhanced with contrast, inhomogeneous due to cystic, necrotic degeneration, and tend to be located in the cerebellar hemisphere or cerebellopontine angle.[25,26]

In children, cerebellar mass with low intensity on T1-weighted MRI image in addition to hyperdensity in CT scan suggests the diagnosis of MB.[27] MRI appearance in adults MB gives a wide range of findings; on T1

weighted, tumors are heterogeneous, hypo or isointense relative on cortex, whereas on T2-weighted image, tumors have hypo, iso, or hyperintense appearance.[28] Hydrocephalus is also a common feature in MB.

Considering these observations, we emphasize that MB should be considered in the differential diagnosis of posterior fossa tumors in all adults, even if the clinical course and radiologic findings seem to be atypical for a MB.

Treatment of MB consists of gross total resection with negative margins followed by radiotherapy

Adjuvant radiation therapy following surgery is the standard of care for managing MB in adult patients with both standard and high risk of recurrence. Conventional dose CSI (30-36 Gy) and boosting the primary brain site in the posterior fossa to 54-55.8Gy with concomitant vincristine and adjuvant lomustine, vincristine, and cisplatin is a favored approach with careful monitoring of toxicities.[29]

Proton therapy is a good option if available to reduce toxicity.[30]

In our case, the persistence of a large tumor residue as well as the delay in initiating radiotherapy adversely affect the prognosis, which has contributed to a rapid progression of the disease despite the use of adjuvant chemotherapy, however it helped to improve the quality of life,

Guidelines regarding the addition of adjuvant chemotherapy to the standard treatment are well established in pediatric literature; while its benefit in adult patients remains controversial because of lack evidence of its efficacy. It is also reported that chemotherapy is less well tolerated in adults justifying dose reduction in most of the patients.

There are no randomized clinical trials comparing radiation therapy to radiation therapy plus chemotherapy in adults to determine the clinical benefit of adding chemotherapy. The use of adjuvant chemotherapy is generally reserved for adults with high-risk disease. A recent retrospective analysis of large cancer database adding chemotherapy to craniospinal irradiation (CSI) showed an overall survival benefit even in patients with M0 disease.[12]

In addition to that, recent studies have demonstrated that postoperative chemotherapy added to radiotherapy improved the prognosis compared with radiotherapy alone.[11,12,14] Franceschi et al.[13] reported that the survival rate at 5, 10, and 15 years in their 7 adult patients who received chemotherapy before radiotherapy was 100%, 100%, and 100% compared with 100%, 78.6%, and 60.2% in patients who received radiotherapy alone, respectively

According to the NCCN guidelines, adult MB patients with high-risk disease (large cell or anaplastic medulloblastoma, disseminated disease within or outside of neuroaxis, unresectable tumors or residual tumors more than 1.5 cm2 post-surgery) are treated with standard dose CSI and posterior fossa radiation with chemotherapy followed by post-radiation chemotherapy. The adjuvant chemotherapeutic regimens widely used are cisplatin or carboplatin and etoposide with or without cyclophosphamide as per a prospective study that reported 5-year PFS rate of 69% `and 5-year OS rate of 75%.[31]

In Our case, we administered chemotherapy to our patient for 2 reasons, because it is a non WNT classic medulloblastoma and the residual tumor post-surgery is more than 1,5cm² which makes it considered as high risk of recurrence.

Second, we reasoned that the addition of chemotherapy to surgery and radiotherapy might contribute to a better prognosis. We used Etoposide Cisplatin as adjuvant chemotherapy protocol which agrees with the guidelines.

Metastases of medulloblastoma frequently occur by CSF dissemination, of which the most well-known are the drop metastases of the cauda equina described as "sugar coating" for their nodular appearance. Hematogenous spread is quite rare now that systemic chemotherapy has been added as the standard of care.[32]

In the setting of recurrence, high dose cyclophosphamide ± etoposide,[33,34] or temozolomide,[35] or oral etoposide or high dose chemotherapy with autologous stem cell transplant,[36,37] are all valid options. Vismodegib, a small molecule inhibitor of Smoothened (SMO) has shown promising activity in recurrent or refractory MB with sonic hedgehog mutations that constitute 80% of adult MB patients,[38,39]

Our patient was treated with Temozolmide due to its availability and its oral use which makes it more convenient.

Regarding the prognosis in adults, the postoperative 5-year survival rate was ~64.9-81.0% and the postoperative 10-year survival rate ~52.0-62.0%, with a median survival time of 8.1-17.7 years.[40]

The prognosis depends on the age, the histological and molecular subtype, the dissemination disease, the persistence of a post-surgical tumor residue and the use of adjuvant radiotherapy and chemotherapy.

CONCLUSION

In summary, our therapeutic strategy of adding chemotherapy to the standard protocol of surgery and CSI failed to eradicate the disease in our patient, as well as he presented an early local recurrence treated with palliative chemotherapy with a notable clinical benefit.

Abbreviations
MB: Medulloblastoma
CSI: Craniospinal Irradiation
PFS: Progression-free survival
OS: overall survival
WHO: World Health Organization
CT: Computed Tomography
MRI: Magnetic Resonance Imaging
Gy: Gray
WNT: wnt signaling pathway
SHH: Sonic Hedgehog
MYC3: Myelocytomatosis oncogene cellular homolog 3

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