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Neuroanatomical Studies

Medulloblastoma with supratentorial and massive extraneural metastasis: literature review in a case documented with 18-FDG PET

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1. Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in childhood. However, its presentation in the adult population is extremely rare, with an incidence reported of < 1% of all brain tumors and 1.5:1 male to female ratio [1,2]. The most common clinical features are those of intracranial hypertension syndrome due to tumor mass effect with concomitant cerebellar signs [3]. Currently, the main treatment modality for MB is surgical resection of the tumor and, an Endoscopic Third Ventriculostomy (ETV) when hydrocephalus occurs. Whenever ETV is not feasible, the placement of a Ventriculoperitoneal Shunt (VPS) has been considered as an alternative in pediatric and adult populations [4,5].

Due to the low incidence of adult MB and the scarce literature on the subject; the dissemination pathways of this aggressive tumor have not been so well-described. Historically, the so-called "drop metastasis" has been the culprit spreading mechanism within the Central Nervous System (CNS). On the other hand, current evidence suggests that VPS plays a key role in extraneural metastases, considering the tumoral cells carriage through the *shut tube device* as the most common pathway to the abdominopelvic organs [6–8]. However, this both mechanisms of metastatic propagation are unable to explain by themselves the massive spreading outside the abdominal cavity, such as retroperitoneal, mediastinal and bone involvement as well.

However, both mechanism of metastatic propagation are unable to explain by themselves the massive spreading outside the abdominal cavity, such as retroperitoneum, mediastinum, and bone involvement as well.

We describe an unusual case of a 31-year-old male with diagnosis of MB who developed thoracic, peritoneal, retroperitoneal, pelvic and bone metastases after the surgical removal of the tumor and the VPS placement for acute obstructive hydrocephalus. To date, only < 300 patients with extraneural metastases have been reported [9]. To our knowledge, this is the only report in literature highlighting 18FDG-PET imaging utility in a case of adult MB with recurrence, metastases dissemination, and poor prognosis.

2. Case

2.1. History and course

A 28-year-old male with unremarkable medical history, who arrived at the Emergency Department (ED) with altered mental status, headache, dizziness and vomiting. Right ipsilateral action tremor and right body lateropulsion characterized by preferential falling to one side were also reported. On physical examination, bilateral papilledema and upward gaze limitation were found with no other cranial nerve deficits. A non-enhanced brain Computed-Tomography (CT) scan (Siemens SOMATOM Sensation 64-slices) revealed a posterior fossa tumor located at the left paravermian region, consequent brain stem displacement, and partial occlusion of the fourth ventricle leading to secondary hydrocephalus (Fig. 1).

2.2. Treatment and follow up

We performed a right pre-coronal ventriculostomy and a middle suboccipital craniectomy – transvermian approach with macroscopic gross total tumor resection (Fig. 1). The histopathology report revealed a Desmoplastic MB/NOS (no molecular study was performed) (Fig. 1).

On the post-operative period, no new neurological deficit was observed, only with persistence of the cerebellar disorders previously mentioned. The patient was discharged home, and received

Abbreviations: **CT**, Computed Tomography; **MRI**, Magnetic Resonance Imaging; **SPGR**, Spoiled Gradient Recalled; **DWI**, Diffusion-Weighted Imaging; **ADC**, Apparent Diffusion Coefficient; **H&E**, Hematoxylin and Eosin; **IHC**, Immunohistochemistry; **NSE**, Neuron Specific Enolase; PET, Positron Emission Tomography

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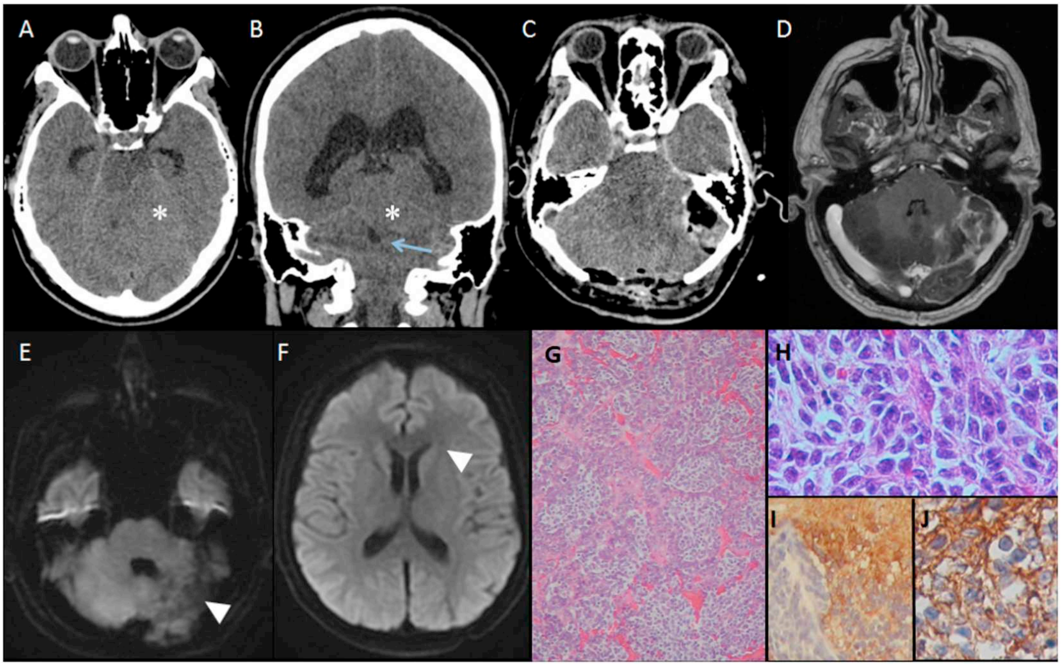

Fig. 1. (A and B) Pre operative brain CT scan and **(C – F)** post operative CT and MRI images. **(A)** axial and **(B)** coronal CT views showing a solid, isodense, infratentorial tumor **(asterisk)** compressing the 4th ventricle **(arrow)**, driving to obstructive hydrocephalus. **(C)** Axial CT view with immediate post-operative posterior fossa changes. **(D – F)** Post operative axial SPGR-and DWI sequences showing no evidence of infra/supratentorial abnormal enhancement and no-diffusion restriction zones **(arrowheads)**. **(G)** Neoplasm of hyperchromic cells, forming nodular, and well-differentiated islands (H&Ex10), **(H)** Tumor close up, demonstrates hyperchromic small cells with scarce cytoplasm and some cellular atypia (H&Ex400). The tumor was **(I)** synaptophysin and **(J)** NSE positive immunoreaction (IHC stain x400).

craniospinal conformational radiotherapy (3D CRT) with daily fractions of 1.8 Gy in 4 weeks (total dose: 36 Gy). A posterior fossa boost was given in a median dose of 19.8 Gy with a fractionated 1.8 Gy daily dose per 2 weeks, employing the linear accelerator (CLINAC C-2100, Varian) with a 6 and 15 MeV energy. Also, adjuvant combined chemotherapy regimen of Carboplatin 450 mg and Vincristine 2 mg monthly was given, both for a total treatment span of 12 months.

After a 3-year follow up, no evidence of supratentorial, infratentorial and spinal active disease on Magnetic Resonance Image (MRI) was demonstrated (Fig. 1). He presented at ED with headache, loss of awareness, psychomotor agitation, and thoracic pain. A neuraxis (brain and spine) MRI was obtained, revealing a left frontal tumor with heterogeneous enhancement and a high Diffusion Weighted Image (DWI) signal. All MRI images were obtained using a 3.0 Tesla magnetic resonance scanner (Siemens) and a 32-channel head coil (Fig. 2). Spine MRI T1 and T1 C+ with fat saturation, also showed multiple vertebral lesions (Fig. 2). Through a dorsolateral craniotomy, a second surgical resection was performed. The hispathological analysis reported the same previous desmoplastic MB lesion (Fig. 2). Radiotherapy and the same chemotherapy regimen were given for another year (Carboplatin 450 mg and Vincristine 2 mg/monthly).

Two months later, the patient developed headache, nausea, vomiting, and urinary retention with increase in abdominal circumference size. A brain and whole body 18-Fluorodeoxyglucose Positron Emission Computed Tomography (18-FDG PET) scan was performed; before radiotracer injection, the patient fasted for at least 4 h. 18F-FDG-PET scans were performed with a Siemens Biograph 64 mCT scanner (Siemens Medical Solutions, Germany). The imaging protocol started with a non-enhanced whole brain CT (100 kVp, 380 mA,) about 45 min after intravenous injection of 299.2 ± 64 MBq (8.1 ± 1.7 mCi) 18F-FDG. Concerning the 18F-FDG-PET information, the studies were analyzed qualitative and semiquantitatively (Syngo-Scenium, Siemens).

Whole body 18F-FDG-PET studies were performed in conjunction with brain scans. 18F-FDG-PET revealed hypermetabolic supra and infratentorial lesions (Fig. 3) as well as an abdominopelvic mass causing bladder and rectum compression. Disseminated lesions with hypermetabolic activity in mediastinum, peritoneum, retroperitoneal, pelvic cavity and bone marrow were also discovered (Fig. 4). Unfortunately, during the hospital stay, the patient presented unfavorable evolution with a fatal outcome 10 days after hospital admission.

3. Discussion

According to the 2016 World Health Organization Classification of Tumors of the Central Nervous System (WHO), all MB are cataloged as very aggressive tumors (WHO IV) either by the histopathology or the molecular diagnostic criteria [2]. The current histopathologic diagnostic criteria describe a tumor with nodularity, extranodular poorly-differentiated cells and intranodular reticulin-free zones with prominent neuronal differentiation. Modern molecular classification additionally establishes four variants of MB: WNT-activated, SHH-activated, group 3 and 4 [2] has been reported to have a more "favorable" prognosis, being more common in adults and less aggressive than the classical variant.

Although controversial, and contrasting with the very aggressive tumoral behavior in this patient, the desmoplastic histologic subtype has been reported to have good prognostic outcome and as being less aggressive than the classic variant [10–12]. Moreover, the desmoplastic

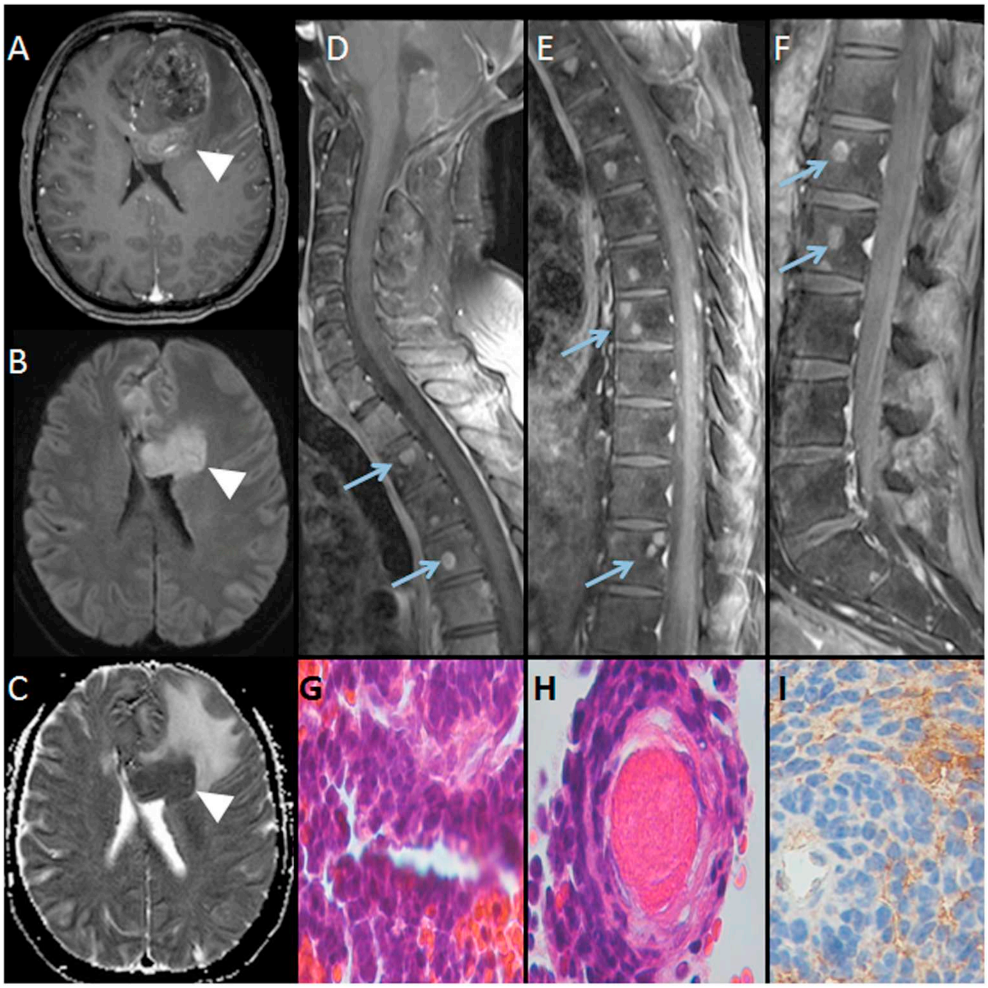

Fig. 2. **(A)** Axial SPGR showing a heterogeneously enhancing left fronto-orbital lesion with periventricular spread to the left frontal horn and accompanying vasogenic edema. Diffusion restriction zones in **(B)** DWI and **(C)** ADC **(arrowheads)**. **(D–F)** Spine MRI fat saturated shows multiple, well delimited and homogeneously enhancing cervical, thoracic and lumbar vertebral lesions **(arrows)**. **(G)** Small, hyperchromatic "blue cells" with perivascular distribution (H&Ex200), **(H)** some vessels show fibrin thrombi. **(I)** Tumor showed synaptophysin and NSE strong positive immunoreaction (H&Ex400).

variant is also the most common histological type, which bears a more "favorable" prognosis compared with the previously known classic, large cell and anaplastic variants [10,11]. Desmoplastic/MB usually presents in the third and fourth decades of life and exhibits the *Sonic Hedgehog-activated (SHH-activated)/TP53-wildtype;* having low propensity to metastasize compared to the other molecular subgroups due to its less aggressive nature [1,3,10,13,14].

MacDonald et al. described a serie of 23 patients with MB formed by 10 metastatic and 13 non-metastatic, interestingly showing that the Platelet-Derived Growth Factor Receptor alpha (PDGFRA) was overexpressed in metastatic MB and was associated with increased migration behavior [15]. Furthermore, specific gene mutations as the *Ptc1* and *p53* were reproduced in animal models, showing a strong relation beetwen more “malignant” and aggressive behavior in the stem cell precursors [16].

Some histological subtypes have shown specific markers from granule cells like neuron-specific enolase, synaptophysin, and nestin [17] supporting the theory of its origin in the oncogenic transformation from granular precursors [18]. Among distinct prevalence between children and adults, there are also differences in clinical, molecular, pathological and treatment aspects related to MB subtypes [1,10,11,13].

Concerning MB metastatic patterns of MB 2 types/varieties have been described: intraneuraxial and extraneural lesions [19]. There are several reports describing supratentorial metastasis; the first of them describes a serie of 13 patients with MB who developed supratentorial dissemination, mainly to the frontal lobe [20]. Other series have documented concomitant supratentorial and spinal propagation of the disease [10,21,22]. One 2015 study analyzed 62 adult patients who underwent surgery, 22 of them (35.4%) developed recurrence in a median time of 47 months (3.9 years). The most common site of relapse was the posterior fossa alone in 8 patients, in 5 of them was both within posterior fossa and spine, and only in 3 of them with supratentorial, posterior fossa and spine involvement as well [3].

The above results are explained by the usual intraneuraxial dissemination pathway, in which focal deposits or metastatic "seedings" are produced by the down-slope gravitational force (e.g. bipedestation) of tumor cells, originate from the “floating” MB cells in the CSF, leading to leptomeningeal spread, a process known as *drop metastases* [2,23].

In patients who have been diagnosed with MB, extraneural

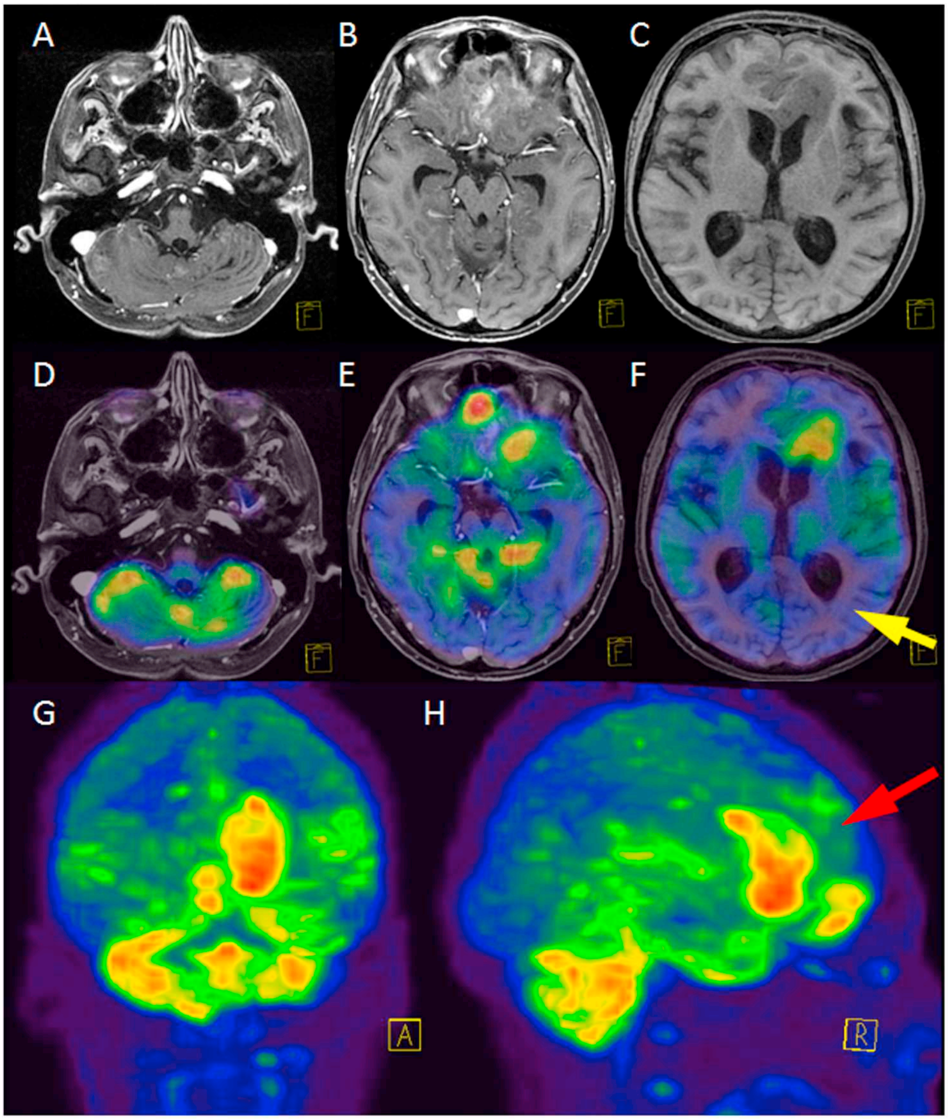

Fig. 3. **(A – F)** Images of PET/T1 MRI + Gadolinium mergers of Software, the studies have a difference of 1 month between them. **(A – C)** MRI + gadolinium, the difference between radionecrosis and the viable tumor is shown. **(D – F)** A significant decrease in brain metabolism is observed **(yellow arrow)**. **(G and H)** Image of maximum intensity of cerebral projection where abnormal and increased uptake of radiotracer showed a lesion in the left frontal region **(red arrow)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

metastases are infrecuently found. Large studies report extraneural metastasis in 2 to 7.1% of cases. However, smaller series report as high as 10–20% [24–26]. On the other hand, only 1% of patients with MB have metastases at initial diagnosis [27,28]. The most common organ for metastatic colonization is bone followed by cervical lymph nodes, whereas thorax, peritoneum and pelvic organs are rarely involved [9,27,29,30].

In the case for supratentorial metastases, it has been suggested that the direct malignant cells seeding happens during surgery after the disruption of the previous intact hematoencephalic barrier [31–33]. Some authors have considered the patient's prone position during surgery or radiotherapy procedures, as an explanation for MB cells depositing in a gravity-dependent fashion at the sub-frontal/cribriform plate region (outside of the radiotherapy target area), as a promoting malignant cell survival and tumor relapse [34].

Specific gene mutations are now associated with increased incidence of metastatic activity in peritoneum and pelvic organs [9,14,16,35]. Nevertheless, patients whose hydrocephalus was treated with VPS, the rate of extraneural metastatic activity is significantly higher. So that the *shunt* itself provides a direct route for systemic spread through abdomen, with faster metastatic colonization of distant organs rates than patients treated without shunt devices (1.3 vs 2 years) [24,25,27,29,31].

Just as it happened in the present case, the extensive abdomino-pelvic dissemination could be totaly explained by the VPS, however, the metastastic spreading mechanism towards bone, bone marrow, mediastinum, and lymph nodes still remains unclear. In Kleinman´s anatomopathological study, vertebral metastases were the most common,

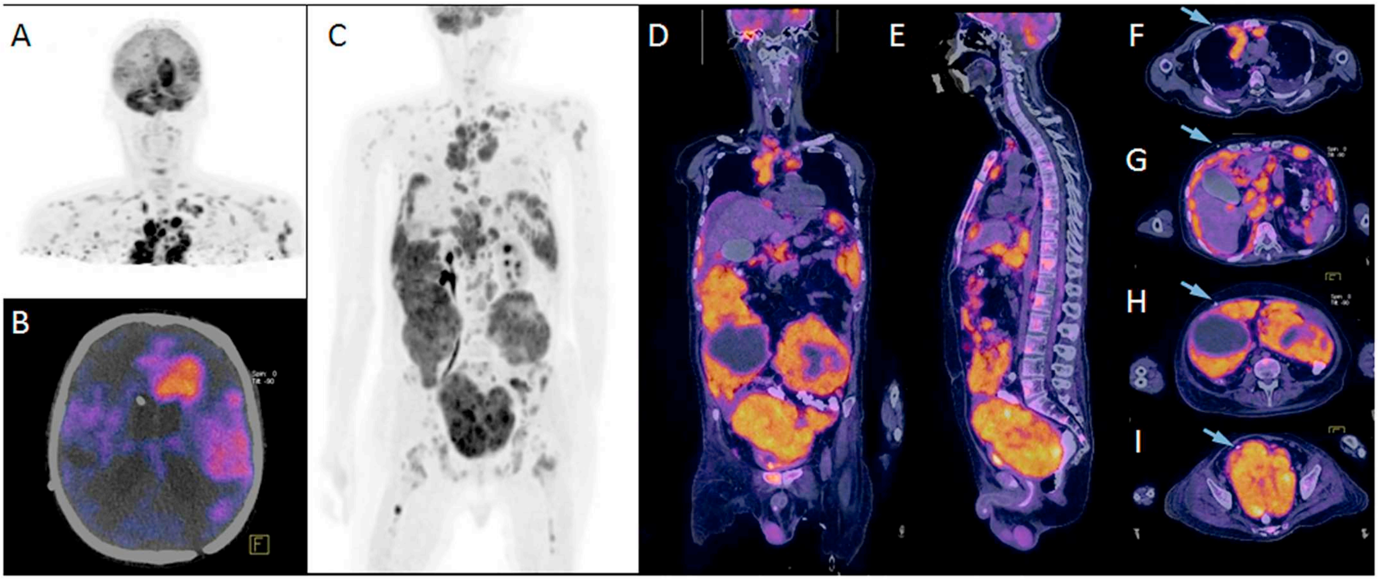

Fig. 4. **(A)** Coronal maximum intensity projections of head and neck and **(C)** whole body PET shows 18FDG-avid cerebral, mediastinal, mesenteric, pelvic and bone implants. **(B)** Axial brain, **(F)** thoracic, **(G and H)** abdomen, **(I)** pelvic, **(D)** coronal and **(E)** sagittal whole body fused PET that corroborates those associated sites with the ventriculoperitoneal shunt **(arrowhead)**.

suggesting a presumably direct dissemination pathway through the medullary canal [6]. Other studies have proposed that skin and neck muscles disruption during surgery, leads to venous and lymphatic spread as a pathway for extra meningeal metastatic dissemination [32,36]. Though craniospinal metastasis from MB currently accounts for one-third of cases, disseminated through the CSF, especially in those who have received radiotherapy and chemotherapy [10]. Rochkind et al. reported the main sites for MB extracranial metastases as: bone in 77% of cases, lymph nodes in 33%, lungs in 17% and muscle and liver in 13% and 10% respectively [29]. Surprisingly, the incidence of just supratentorial metastasis has not been estimated yet.

As for the diagnostic imaging studies available in MB, lesions with elevation of *N*-acetyl-aspartate and choline/creatine ratio in spectroscopy, hyperintensity in diffusion (ADC low value as $0.689 \times 10{-}3\,mm2/s$) and perfusion MRI sequences (maximal relative cerebral blood volume (rCB-Vmax)) of 2, were highly suggestive of MB diagnosis over other neoplasms [37].

Regarding PET scan, it is well known that 18F-FDG crosses the blood-brain barrier and it is actively transported inside the cells where it is phosphorylated; therefore, 18F-FDG uptake is generally associated with higher malignant behavior in high-grade tumors [38,39].

Despite of the fact that the prognostic value of 18F-FDG uptake has been well established, other authors have demonstrated its diagnostic limitations owing to the high rate of physiologic glucose metabolism in normal brain tissue. However, the detection of tumors with only modest increases in glucose metabolism is difficult even in some cases of high-grade tumors [40,41].

The utility of PET-scans in brain tumors has been mostly demonstrated in MB, rendering it useful in establishing prognosis, as well as probability of malignant behavior [42,43]. This is a remarkable statement, since the recent world-wide employment of PET images, it is possible to identify sites of metastatic disease such as intraneuraxial and, more importantly, extraneural dissemination prior to surgery and adjuvant therapies. Knowing that detection of skeletal involvement or other metastatic colonization of distant organs is the prime cause of mortality in patients with MB, should provide possible future treatments for this dynamic and aggressive disease [44].

4. Conclusion

Although the histological MB variants are directly related to clinical behavior and prognosis, this is an atypical presentation of desmoplastic MB. The histopathological classification remains still useful due to their clinical utility when the molecular analysis is limited or not feasible.

A close short and long-term follow-up in patients with MB is of the outmost importance, particularly after any surgical intervention. The initial clinical approach to patients with MB should include complete brain image studies; as well as histopathological, genetic and molecular tumor features are mandatory to assess the clinical attitude, treatment, and prognosis.

The precise metastatic pathways are still unclear; therefore, more studies are needed to elucidate them. A complete workup at initial diagnosis is mandatory to rule out early intra and extraneural metastasis.

18FDG-PET is a very useful tool to identify residual or tumor recurrence, and could be considered as an important diagnostic image tool for early detection of MB metastases. To our knowledge, this is the only report in current literature about the utility of 18FDG-PET imaging in a case of adult MB.

Conflict of interest

We all declare that we have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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All the authors have contributed substantially to design, realization, analysis, and presentation of the this work. Each author has reviewed and approved the content of this writing for publication. This authorization has being dictated by the author of correspondence, as well as by each one of the authors.

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