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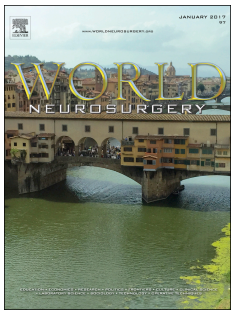

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professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Keywords: rhabdomyosarcoma, brain tumor, metastasis

ABSTRACT

Background: Rhabdomyosarcoma (RMS) is a rare malignant tumour originating from striated muscle cells; it accounts for only 3% of all soft tissue sarcomas in adults and its metastases can also reach the central nervous system. Only sporadic cases of primary brain RMS (PBRMS) have been reported so far.

Case presentation: We discuss the atypical presentation and diagnostic challenge of PBRMS in a 65-year-old man. He presented with a 3-day history of progressive right hemiparesis caused by an unspecific left fronto-parietal heterogeneously enhancing lesion. Total body CT and Positron Emission Tomography (PET) scans performed at baseline did not reveal other secondarisms. Patient underwent radical excision of the lesion, which allowed to establish the diagnosis, with immunohistochemical staining positive for desmin and myogenin. Stereotactic radiotherapy guaranteed local disease control; nonetheless the patient required also adjuvant chemotherapy when he developed large right lung metastases 6-months postoperatively.

Conclusions: PBRMS can be hardly distinguished from other malignant brain tumours during preoperative radiologic workup; only histology can raise the suspicion of primary or metastatic rhabdomyosarcoma, depending on the presence of other distant lesions. Our review of the literature demonstrates that prognosis is poor: 44% of patients die within one year from diagnosis. Overall survival seems to correlate with radical resection, tolerance of stereotactic or if necessary full neuraxis radiotherapy and adjuvant chemotherapy. Given the high relapse rate close monitoring and re-staging are imperative.

INTRODUCTION

Rhabdomyosarcoma (RMS) is a rare malignant tumor arising from striated muscle cells, and accounts for only 3% of all soft tissue sarcomas in adults. Of note, more than 50% of all RMSs are diagnosed in the pediatric population: in fact, they account for roughly 20% of all tumors in children below 3-years of age. Of note, only sporadic cases of primary brain rhabdomyosarcoma (PBRMS) have been reported so far, in fact most of the central nervous system localizations are usually metastatic. In this report we present a new case which to the best of our knowledge constitutes the 18th case of PBRMS in adults and the 3rd case who developed distant metastases during follow up [1–16]. This atypical presentation will serve as the basis to critically revise the current literature on PBRMS: we will discuss the complexity of formulating the right diagnosis and optimize adjuvant treatment and postoperative follow up of patients harbouring these rare lesions.

CASE DESCRITION

History: We report the case of a 65-year-old man who presented to our A&E Department with a 3-day history of progressive right hemiparesis and confusion. Urgent CT head revealed a heterogeneous contrast-enhancing left fronto-parietal lesion surrounded by remarkable edema suggestive of either a metastatic or a high-grade primary brain tumor. The Total Body CT and PET scans did not reveal any other visceral lesion thus delegating the task to reach a definitive diagnosis to the neurosurgical team.

Treatment: Given the rapid onset of neurological symptoms, and the CT findings typical of a solid lesion rather than a cerebral lymphoma, high-dose steroids were started and surgery expedited. Surprisingly the preoperative brain Magnetic Resonance Imaging (MRI) realized within few days for image-guided surgery purposes showed progressive volumetric increase of the lesion (Figure 1). Excision was microsurgically radical and the perioeprative course

uneventful; with great surprise the intraoperative impression was that of a sarcomatous lesion. An MRI brain performed within 24 hours from surgery showed no residual tumor, and the patient was safely discharged home on the third postoperative day.

Histopathology: The tissue demonstrated a diffuse infiltration and proliferation of cells with a very pleomorphic nucleus, coarse chromatin and cytoplasm, as well as cells with large nuclei and abundant eosinophilic cytoplasm giving them a rhabdoid appearance (Figure 2). These neoplastic elements were arranged in intersecting bundles in all directions with a striking perivascular tropism. In line with the neurosurgical suspicion the initial histology examination was in keeping with a RMS appearance. The pathology team proceeded with additional immunohistochemical staining which revealed diffuse and strong expression of desmin, myoD1, and more focally myogenin (about 30%). Given the above, the conclusive diagnosis of PBRMS of embryonic type was made.

Clinical evolution: The case was discussed in our multidisciplinary neuro-oncology meeting and given the malignant nature of this lesion the consensus was in favor of a stereotactic radiotherapy of the tumor bed (33 Gray).

At 6 months follow up, the patient developed a progressive right chest pain and a CT scan showed a large right lung mass (Figure 3). The patient underwent CT guided biopsy suggesting a PBRMS metastasis. A restaging of the disease with Total-Body CT scan showed no other secondarisms and the patient responded well to adjuvant chemotherapy with VAC protocol consisting in vincristine, dactinomycine and cyclophosphamide. At 1 year from diagnosis the patient reported a generalized well-being, with good performance status (ECOG 1) and the re-staging did not rule out recurring brain tumor or any new distant progression of the disease elsewhere.

DISCUSSION

The literature review on PBRMS confirmed the paucity of information available on this class of tumors, which have been only sporadically reported (see Table 1). PBRMS are typically found in young adults, with an age at time of diagnosis ranging from 20- to 65-year. PBRMS are considered as composite rhabdoid tumors, which are well-established neoplasms with rhabdoid features; this class includes also rhabdoid meningiomas, rhabdoid glioblastomas, carcinomas and sarcomas with rhabdoid features [19]. The histological features, firstly characterized by Biggs et al. [20] are pretty specific: PBRMS usually appear as diffuse lesions composed by homogeneous, large, round or polygonal neoplastic cells, densely packed and sometimes arranged in columns, with eccentrically located nuclei and abundant, eosinophilic cytoplasm. Similarly to any other high

grade tumors of the central nervous system, PBRMS typically demonstrate frequent mitotic figures, noteworthy they are characterized by unspecific features, such as positive immunostaining for ki-67 proliferative labeling index, and more specific ones, such as in our care, with a strong reaction for epithelial membrane antigen, vimentin, desmin, myoD1, and more focally myogenin [2,21]. Furthermore, a remarkable trait of malignant RMS regardless of their primary location, is the inactivation by deletions and/or mutations of a tumor suppressor gene, SMARCB1/INI1, located in chromosome band 22q11.2 [19,22] hence genetic diagnosis is becoming the new rule [23].

Similarly to the case presented in this article, the preferential localization of these lesions is anywhere in the supratentorial space, although it appears that the frontal and parietal lobes are those more frequently involved (roughly 62% of the cases). In few cases authors noticed a tendency to leptomeningeal spreading, whereas an extracranial dissemination of PBRMS had always been considered a rather exceptional event and described only twice before the present report. This

behavior is similar to other sarcomatous lesions (including gliosarcomas, intracranial solitary fibrous tumors, etc) [17,18], and certainly highlights the relevance of our case, explaining the complexity of reaching a conclusive diagnosis and addressing the clinical challenges of such rare and atypical presentations in the absence of well established international guidelines. In fact, the management of PBRMS is often based on the individual expertise of the many specialists involved; from a neurosurgical perspective radical excision should always be attempted whenever safely achievable, keeping in mind that complete microsurgical resection alone is not enough to guarantee the best possible outcome. The surgical strategy should be tailored not to incur in any medical or surgical perioperative complications, and aimed to expedite stereotactic radiotherapy/radiosurgery on the tumor bed within few weeks [1,4,8,24]. While most authors are focusing on local gammaknife or cyberknife treatment as described in our case, the majority of reports conclude that regardless of the modality the radiation dose administered should be the same considered for

malignant gliomas [2, 4-9, 11-16, 25]. Efforts to delay radiation - especially attempted in pediatric cases to spare children from radiation-induced side effects - often fail; our review of the literature suggests that longer overall survivals are frequently attained in isolated PBRMS patients treated with a combination of radical surgery and stereotactic radiosurgery/radiotherapy plus redo surgery and second stage cranio-spinal radiotherapy in case of local recurrence/spreading [2,5,6,9]. Since previously reported cases are scattered across more than 3 decades of scientific literature, the role of chemotherapy regimens is also debatable: on one hand we lack a consensus on the need for adjuvant chemotherapy, on the other hand, owing to the heterogeneity of applied cytostatic agents, a comparison of effectiveness is not even possible. In our patient the decision to eventually consider VAC regimen was taken following discussion of the case with a national center of excellence for the care of rare soft tissue tumors.

Our review of the literature demonstrates that PBRMS prognosis is poor, although overall survival is reported to range from 4 months to 6 years [1–16], 44%

of patients die within one year from diagnosis. Unfortunately, given the paucity of cases reported, no specific prognostic factors have been identified; as such this additional case represents a substantial contribution to increase the current knowledge about this class of tumors. Going forward, more potential therapeutic targets emerging from a better understanding of the biological mechanisms of tumor growth will help to determine the appropriateness of new chemotherapy regimens, small molecule inhibitors and stem cell rescue [19, 26-29]. To this regard, it is worth mentioning the importance of joint projects such as the establishment of EU-RHAB, a registry on rhabdoid tumors, to generate transnational databases and to favor standardization of treatment regimens as the basis for novel phase I/II trials [30]. Until new protocols will be made available, we feel appropriate to stress the importance of a strict clinical and radiological follow up, bearing in mind that any red flag for metastatic disease should prompt oncological referral and immediate systemic re-staging.

Declarations

Ethics approval and consent to participate :

Not applicable

Consent for publication :

Not applicable

Availability of data and materials :

Not applicable

Competing interests :

Not applicable

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Authors' contributions :

This is to certify that all authors have participated in the present study including its conception, writing and critical revision.

LEGENDS :

Figure 1 : Pre-operative T1 a) axial, b) sagittal , c) coronal MRI showing a large left frontoparietal heterogeneously enhancing lesion.

Figure 2 : Photomicrographs showing rhabdomyosarcoma colored with Haemotoxylin and Eosin (A) and immunostained with antibodies to MyoD1 (B) and myogenin (C) : Proliferation of highly pleomorphic tumoral cells with abundant eosinophil or nucleated cytoplasm with focal rhabdoid appearance (surrounded) (Haematoxylin and eosin x20) (A) , Diffuse nuclear in favor of MyoD1 expression (x20) (B) and focal nuclear for myogenin (x20) (C)

Figure 3 : Postoperative six months total BodyCT scan demonstrating a large lobular mass in the right apex compatible with secondary lesion of rhabdomyosarcoma.

Table 1. Primary brain rhabdomyosarcoma : review of the literature

Legends table 1 : Act: Actin, Alpha1 chy: Alpha1 Chymotrypsin, B: Biopsy, Des: Desmin, EMA: Epithelial Membrane Antigen, F: Female, GFAP: Glial Fibrillary Acidic Protein, Ker: Keratin, L: Left, M: Male, Myo: Myosine, Myog: Myogenin, Myogl: Myoglobuline, NA: No Available, NSE: S100, R: Right, S: Surgery, SMA: Smooth Muscle Actin, Syn: Synaptophysin, Vim: Vimentine

*****Indicates the patient was alive at the time of writing

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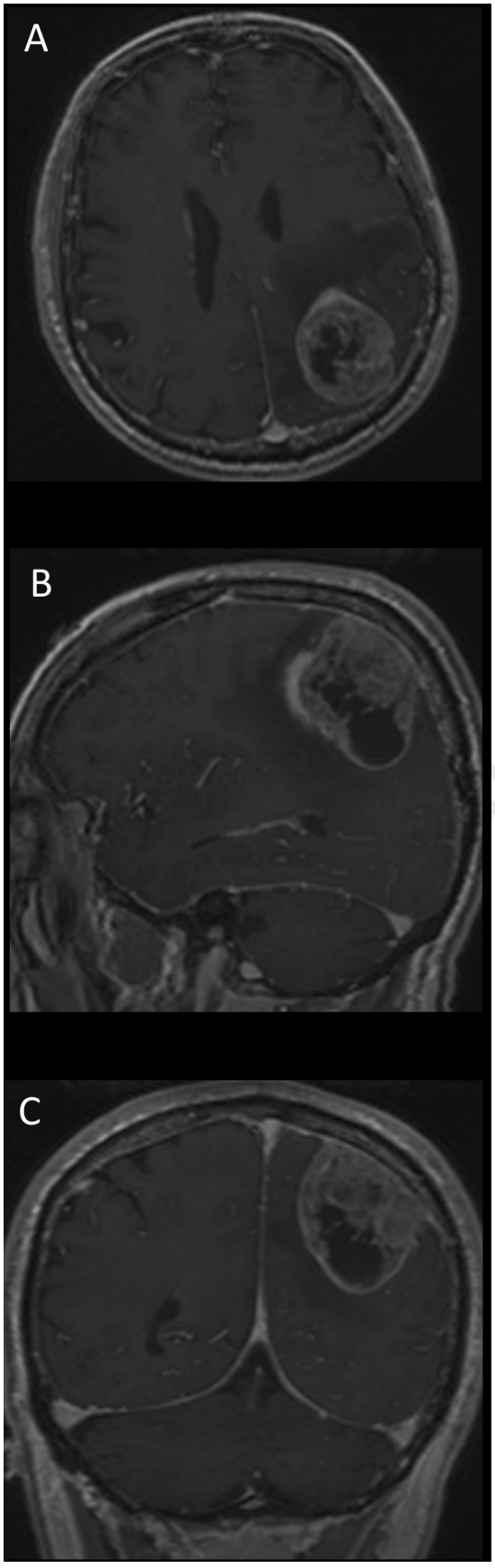
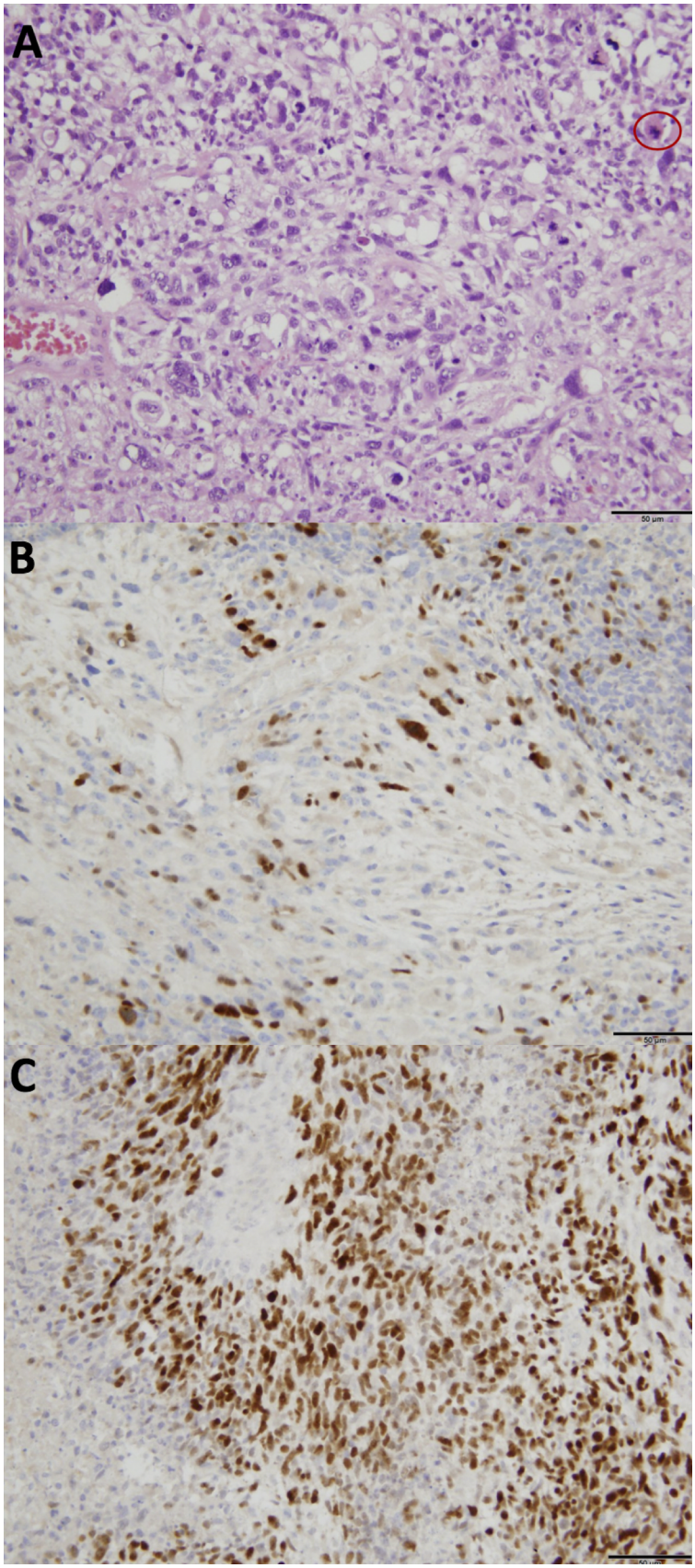
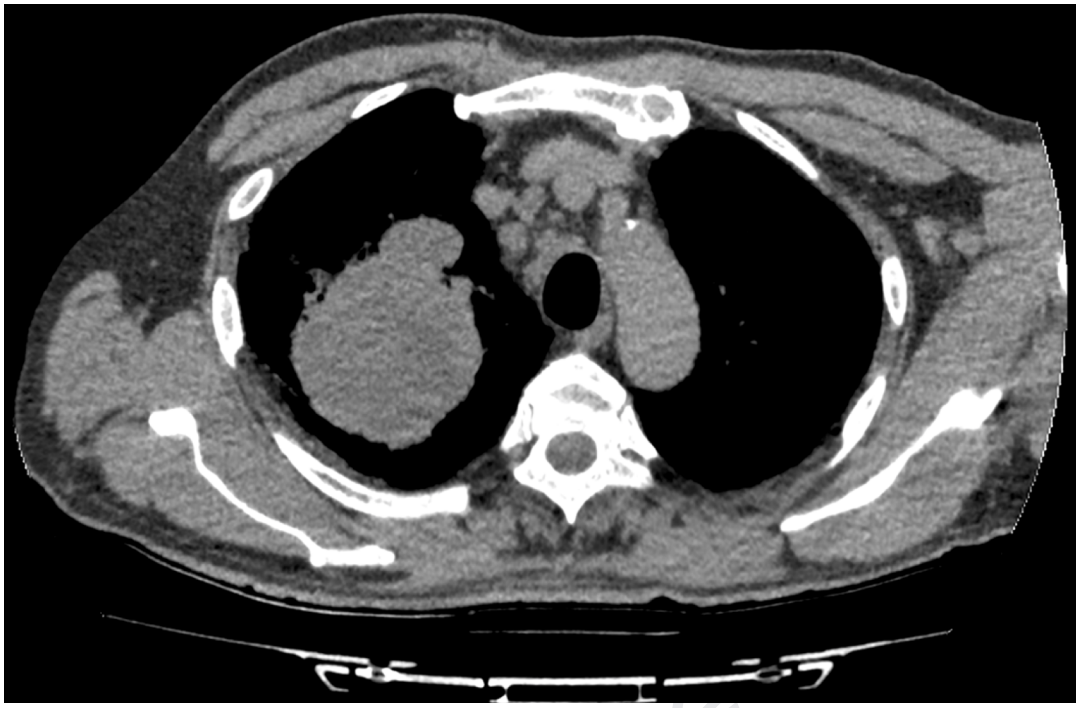
	Reference	Age	Sex	Tumor location	Surgery	Adjuvant therapy	Metastasis	Survival (months)	Hic staining positivity
1	Leedham et al. 1972	45	F	R frontal	S	None	No	10	Act, Myo
2	Horn et al. 1992	21	M	L temporal	S	Radiation	NA	72	Vim, EMA, Alpha1 chy
3	Fisher et al. 1996	32	M	L frontal	B	None	NA	5	Vim, GFAP, S100
4	Ashraf et al. 1997	34	M	L parietal	B	Radiation	NA	6	Vim
5	Celli et al. 1998	46	M	R fronto-parietal	S	Radiation, Chemotherapy	No	30	Myo, Myog, Act
6	Sugita et al. 1999	27	M	Pineal	S	Radiation, Chemotherapy	Pulmonary site	24	Vim, EMA, Syn, NSE, S100, SMA
7	Byram et al. 1999	35	M	L temporal	S	Radiation	No	60	Vim, EMA, Ker
8	Arrazola et al. 2000	20	M	L parietal	S	Radiation	No	24 *	Vim, EMA, ker, S100
9	Pimentel et al. 2003	31	F	R parietal	S	Radiation, Chemotherapy	Carcinomatous Meningitis	6*	GFAP, Vim, Alpha1 antitry
10	Erickson et al. 2005	20	F	R occipital	S	None (pregnancy)	No	Total removal	GFAP, Vim, EMA
11	Grebe et al. 2008	40	F	L frontal	S	Radiation	No	11	Act, Des
12	Mirone et al. 2009	27	F	L frontal	S	Radiation, Chemotherapy	No	14 *	SMA, EMA
13	Pirillo et al. 2011	51	F	L parietal	S	Radiation	No	20	Syn, Vim, Des
14	Palta et al. 2011	44	M	L fronto-parietal	S	Radiation, Chemotherapy	No	NA	Myo, Des, Myogl
15	Caporlinghua et al. 2014	50	F	R cerebellopontine angle	S	Radiation, Chemotherapy	Cervical paravertebral muscles, Upper mediastinum	7	Myog, Des
16	Lau et al. 2015	33	F	Pineal	S	Radiation, Chemotherapy	Carcinomatous Meningitis	5	MyoD1, Myog, Des
17	Scull et al. 2016	43	F	Pineal	S	No	No	4	Des, Act
18	Present patient	65	M	L fronto-parietal	S	Radiation, Chemotherapy	Pulmonay	12*	Des, MyoD1, Myog







List of abbreviations:

CT : Computerized Tomography

ECOG : Eastern Cooperative Oncology Group

EU-RHAB: European Rhabdoid Registry

MRI : Magnetic Resonance Imaging

PBRMS : Primary Brain Rhabdomyosarcoma

PET : Positron Emission Tomography

RMS : Rhabdomyosarcoma

VAC protocol : Vincristin, Dactinomycin, Cyclophosphamide protocol

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication :

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Authors' contributions :

This is to certify that all authors have participated in the present study including its conception, writing and critical revision.