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Review article

Primary cerebellopontine angle melanoma: Case Report and Systematic Review



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ABSTRACT

Introduction: Primary cerebellopontine angle melanoma (PCPAM) is one of the most rare primitive brain tumors. Its management and prognosis are drawn from very few published cases.

Aim: The aim of this study was to provide an approach to help practitioners diagnosing similar cases.

Material and methods: A systematic review was conducted. A PCPAM case is also presented. **Results:** The search yielded 13 cases of PCPAM (53% were males) with a median age of 32 years (range 26–56 years). The most frequent symptoms were hearing loss (77%) and ataxia (62%). All underwent neurosurgical removal of the tumor due to worsening of symptoms. Post-surgery follow-up showed that only half of the cases had free-of-disease survival beyond a year. The other half had a poor outcome few months after surgery. We present a 77-years-old female patient with PCPAM with clinical characteristics different from those described in the literature.

Discussion: Results indicate that diagnosis criteria are still lacking specificity. Therefore, clinical features have led clinicians to reconsider the diagnosis more than once. New techniques, such as PET-scan and genetic analysis can greatly assist in the search for the primary tumor. Nowadays, complete resection and radiotherapy are still the gold standard treatment. Prognosis differs between the cases, but age and tumor biology are the main indicators of survival.

Conclusions: We strongly suggest strengthening the surveillance of patients with PCPAM as the management and prognosis differ significantly from those with metastatic melanoma.

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1. Introduction

Primary melanocytic lesions arising from central nervous system (CNS) include localized lesions presented as leptomeninges masses that can be benign tumors (e.g. melanocytoma); melanocytic tumors of intermediate differentiation (MID); and malignant ones, such as melanoma.¹ Primary cerebellopontine angle (CPA) melanoma (PCPAM) only represents 1% of all human melanoma tumors.² The incidence has been estimated to be 0.005 cases per 100 000 but we lack stringent diagnostic criteria for its calculation.

CPA is a rare site for tumors as it represents 6%–10% of all intracranial tumors.³ The most frequent mass lesions of the CPA region are vestibular schwannomas and meningiomas, while melanocytic lesions appear to be a very uncommon finding.⁴

Bailey first described PCPAM in 1948.^{5,6} Since then, few cases were reported in the literature. To date, diagnosis remains on exclusion of a primary malignant lesion outside the CNS. Clinical presentation and auxiliary test results may differ among patients receiving this diagnosis. Therefore, the real origin of this tumor is uncertain. The low number of existing published case reports also reveals a lack of evidence-based guidelines for the management of PCPAM.⁷

2. Aim

The aim of this study was to review PCPAM cases and studies published in the literature, in order to guide practitioners managing similar cases. Additionally, we present a case report of a PCPAM, as an instance of this condition.

3. Material and methods

A systematic review of the literature was conducted in Medline, Embase and central databases with the terms 'melanoma,' 'brain tumor,' 'cerebellopontine angle' and their MeSH-term synonyms. The search was restricted to English publications from 1948 to 2013. Non-published studies were collected after tracing down references of the included studies. The selection criteria included PCPAM: (a) case reports; (b) systematic reviews and/or meta-analysis; and (c) clinical trials in which any interventions, drug or surgical, were tested. If multiple studies reported similar results, a selection was made to minimize redundancy. After scrutinized titles and abstracts, we retrieved full text of those that met the selection criteria. Then, we independently extracted the data to a standard form that focused on demographic data, symptoms and signs reported; imaging, surgical and pathological findings; and finally treatment and prognosis reports of the patients with this tumor. We performed quantitative analysis and qualitative analysis depending of the variable nature. We used the Microsoft Excel 2011 version 14.1.0 and STATA 12.0 for both analyses. Figures were designed with Review Manager (RevMan) version 5.2.

Numerical data are presented in percentages, median and 25% and 75% percentiles due to the skewed distribution

of the variables and the small sample. Qualitative data are described in Table 1. A meta-analysis was not performed because of the heterogeneity and shortage of reports. This study was conducted according to the recommendations of the Cochrane Collaboration,⁸ and is reported following the Prisma Statement.⁹

4. Results

The search yielded 58 studies, and after abstract screening, 13 matched the selection criteria. Then, 2 studies were excluded due to language issues (articles in French). Finally, 11 studies were included involving 13 cases of PCPAM for the review (Fig. 1). Those 13 cases of PCPAM were included in the qualitative and quantitative analysis (Table 1).^{10–13}

The median age of subjects was 32 years old (26–56 years old); 54% were male; and the median timing from onset of symptoms to presentation into the hospital was 5 months (2–48 months), with a range of 1 month to 15 years.

The most frequent symptoms and signs presented in patients with PCPAM (Table 2) were unilateral hearing loss (77%), ataxia or gait unsteadiness (62%), unilateral facial palsy (46%) and headache (38%).

Magnetic resonance imaging (MRI) was the preferred imaging technique used in the diagnosis beyond 1990.¹⁴ The most recurrent findings were T₁- and T₂-weighted hypointense mass (64% and 55%, respectively).

All the cases underwent neurosurgery due to worsening of symptoms. The most frequent surgical technique to approach the tumor was suboccipital and translabyrinthine craniotomy (23% each). The most frequent intraoperative findings reported the tumor to be a black (69%), highly vascular (62%), and tough (30%) mass. Total resection of the tumor was reported in 46% of the cases.

The pathology findings followed a similar profile, consisting of large, polygonal and pleomorphic cells, arranged in nest or sheets, with vesicular, large and central nuclei and prominent nucleoli. Almost all the tumors showed a high-mitotic rate (only one did not¹⁵). In total, 54% of reports used positive staining with both HMB45 and S-100 stains as confirmation of the melanocytic origin of the tumor, consistently after 2001 (Table 1).

Methods for the study of a primary origin of the tumor outside the CNS were diverse; 69% reported a dermal and ophthalmologic evaluation, while 23% used one of these imaging techniques: chest X-ray, abdominal ultrasound, PET-scan, CT-scan, Bone-scan.

In 10 cases (77%) patients received radiotherapy after surgery. The other 3 (23%) ones did not: (1) because the tumor had benign behavior¹⁵; (2) because complete resection of the tumor,¹⁶ and (3) because the patient died 5 days after surgery of post-operative complications.¹⁷ One patient was treated with temozolomide adjunctive to radiotherapy.

The follow-up report showed that 46% of patients had a long free-of-disease survival period, from 1 to 8 years after surgery. Conversely, 46% of the patients died within 1–10 months and had a median survival period of 4 months after hospital discharge.

Table 1 – Clinical features of primary CPA melanoma reported in the literature: M – male; F – female; m – months; NR – no reported; N – None; MRI – magnetic resonance imaging; PET – positron emission tomography; US – ultrasound, HyperI – Hyperintense; HypoI – Hypointense; IsoI – Isointense; CR – complete resection; RT – radiotherapy; TMZ – temozolomide.

Case report	Sex	Age	Symptoms and signs	Duration (m)	MRI findings		Surgical findings (CR)	Immunopathology stain	Surveillance evaluation	Therapy	Follow-up
					T ₁	T ₂					
Bhandari et al. 2012 ⁵	M	29	Hearing loss, vertigo, loss of taste, ataxia, facial palsy, nystagmus	5	HyperI	HypoI	Suboccipital craniotomy, black, firm and tough lesion (No)	NR	PET-scan, US abdomen, chest X-ray, Clinical evaluation	RT	Death 12 months
Wadasadawala et al. 2010a ⁷	M	21	Dizziness, generalized tonic-clonic seizure	1	HyperI	HypoI	Temporo-parietal craniotomy, black highly vascular tumor (No)	S-100, HMB45 positive, MIB-1 9%–10%	PET-scan	RT	Death 1 month
Wadasadawala et al. 2010b ⁷	M	24	Headache, tinnitus, hearing loss	2	HyperI	HypoI	Retromastoid craniotomy, black, highly vascular lesion. (No)	NR	PET-scan, Bone-scan, US, chest X-ray, Clinical evaluation	RT	NR
Brackmann and Doherty 2007a ¹⁰	M	42	Facial palsy, headache, hearing loss, tinnitus, vertigo, loss corneal reflex	180	NR	NR	Transcoclear craniotomy, black, highly vascular lesion, adherent to brainstem. (No)	S-100, HMB45, Vimentin positive.	No report	RT	Free-of-disease 8 years
Brackmann and Doherty 2007b ¹⁰	F	56	Hearing loss, vertigo, facial palsy	3	IsoI	HyperI	Translabyrinthine craniotomy, black, quite vascular lesion. (No)	S-100, HMB45 positive	Bone-scan, CT-scan, Clinical evaluation	RT	Death 2 months
Oluigbo et al. 2006 ¹¹	M	75	Hearing loss, ataxia, dysarthria, headache, diplopia, dysmetria, dyssynergia	4	HyperI	HypoI	Suboccipital craniotomy, dark, hemorrhagic, adherent to tentorium mass. (Yes)	Masson Fontana, S-100, HMB45 positive	CT-scan, Clinical evaluation	RT	Death 10 months
Piedra et al. 2006 ¹²	M	49	Dizziness, loss of taste, nausea, vomiting, hearing loss, decrease corneal reflex and facial sensation, ataxia, nystagmus, facial palsy	84	HyperI	HyperI	Translabyrinthine craniotomy, friable, dark tumor (No)	S-100, HMB45, Tyrosinase and Melan A positive. MIB-1 6.5%	PET-scan, Clinical evaluation	RT, TMZ	Death 6 months
Kan et al. 2003 ¹⁵	F	26	Ataxia, Hearing loss, Dysphagia	NR	HyperI	IsoI	Transcoclear craniotomy, black, avascular lesion, adherent to IX, X and XI cranial nerves (Yes)	S-100, HMB 45 positive MIB-1 less than 1%.	CT-scan, Clinical evaluation	N	Free-of-disease 12 months

Desai et al. 2001 ¹³	F	17	Headache, Vomiting, Diplopia, Ataxia, III and V cranial nerves paresis, cerebellar signs	1	HyperI	HypoI	Subtemporal craniotomy, Black, elastic, vascular tumor (Yes)	Masson Fontana positive	Barium enema, US abdomen, chest X-ray, Clinical evaluation	RT	Free-of-disease 12 months
Whinney et al. 2001 ¹⁶	F	29	Hearing loss, Facial palsy,	48	NR	HypoI	Translabyrinthine craniotomy, black, encapsulated tumor (Yes)	S-100, HMB45 positive	MRI head and neck	N	Free-of-disease 18 months
Vasdev et al. 1990 ¹⁴	F	56	Visual disorder, Unstable gait, Nausea	6	HypoI	HyperI	Large dark tumor, deeply embedded into the cerebellum (No)	NR	Clinical evaluation	RT	Free-of-disease 36 months
Braga et al. 1989 ¹⁷	F	72	Vertigo, Hearing loss, Ataxia, Vomiting, Mental deterioration	18	NR	NR	Posterior fossa craniotomy, dark, highly vascular, encapsulated tumor (Yes)	Iron pigmented negative	Clinical evaluation	N	Death 5 days
Narayan et al. 1981 ³⁷	M	32	Ataxia, Headache, Diplopia, Vomiting, Nystagmus, Hearing loss, Ptosis, VI and VII cranial nerves paresis, diminished corneal reflex, Papilledema, dysmetria, dyssynergia, Lethargy	2	NR	NR	Suboccipital craniotomy, black, invasive, hemorrhagic, adherent to tentorium tumor. (Yes)	NR	Bone-scan, Clinical evaluation	RT	Free-of-disease 18 months

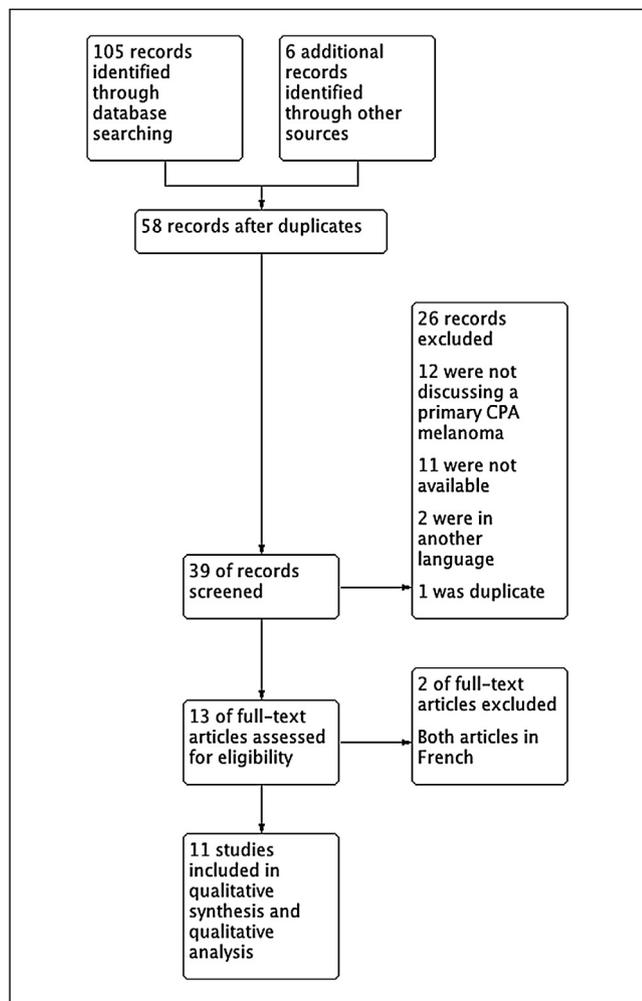


Fig. 1 – Selection of studies: only the first reason for exclusion is reported.

A 77-year-old woman with one-month history of severe occipital headache, dizziness and vomiting was admitted to the neurosurgical service of our hospital in August 2010. On the physical examination, her higher mental status was impaired: she was oriented to person only. In the neurologic exam, she had gait instability, muscular hypotonia in the arms but more marked in the legs, bilateral intention tremor (evaluated with nose-index, ear-index, heel-knee tests), bilateral diadochokinesia, dysarthria and right nystagmus. CT revealed a hyperdense mass of 30 × 24 mm on the right cerebellopontine angle with perilesional edema; the MRI exposed heterogeneous isointense lesion with a hyperintense halo in T₁-weighted protocol (Fig. 2a), and slightly hyperintense in T₂-weighted protocol. The patient underwent neurosurgery and the lesion was boarded with a right retrosigmoid craniotomy. A blackish indurate tumor was found, which was highly vascularized. The resection was partial. The pathology reported polygonal nest of cells, large oval central nuclei, eosinophil cytoplasm with heterogeneous melanin content (Fig. 2b), high-grade mitotic rate and positive reaction for S-100 and HMB-45¹⁸ (Fig. 2c and d).

Table 2 – Frequency of symptoms and signs of primary CPA melanoma cases reported in the literature (N = 13 patients).

No.	Symptom	%
1	Hearing loss	76.92
2	Ataxia	61.54
3	Facial palsy	46.15
4	Headache	38.46
5	Vertigo	30.77
6	Diplopia	30.77
7	Vomiting	30.77
8	Nystagmus	23.08
9	Corneal reflex deficit	23.08
10	Loss of taste	15.38
11	Dizziness	15.38
12	Tinnitus	15.38
13	Dysmetria	15.38
14	Dyssynergia	15.38
15	Nausea	15.38
16	Mental deterioration	15.38
17	Seizures	7.69
18	Tympanic mass	7.69
19	Slurred speech	7.69
20	Ptosis	7.69
21	Papilledema	7.69
22	Hemi-facial sensorial deficit	7.69
23	Dysphagia	7.69
24	Paresis III cranial nerve	7.69
25	Paresis V cranial nerve	7.69
26	Paresis VI cranial nerve	7.69

Afterwards, ophthalmology, dermatology and gastroenterology departments evaluated her for staging and the existence of an extracranial melanotic primary tumor. After an exhaustive search, the neurosurgical team made the diagnosis of PCPAM, initiating isolated radiotherapy. However, the patient died 2 months after discharge.

5. Discussion

The neural crest origin of melanocytes and their migration to the leptomeninges and pineal gland explain the rise of melanocytic lesions within the CNS. Although the CNS is the third common site for melanoma metastasis, after breast and lung carcinomas; metastatic lesions to the CPA from malignant melanoma account for only 0.2%–0.7% of the lesions in this site.¹⁰ PCPAM tumors are even more rare.

This review yielded only 13 cases of PCPAM published in English. There was not any other type of publication. The scarce number of studies indicates the need for increase research on the topic, and assess the results with caution.

One of the earliest reviews of melanocytic lesion in the CNS was from Terao et al.¹⁹ Furthermore, Brat et al.²⁰ described 33 cases of primary melanocytic neoplasm of the CNS: 13 (40%) had malignant melanoma and only 2 patients (6%) had PCPAM. Bhandari⁵ listed 17 PCPAM cases reported in the literature, from Bailey P^{5,6} in 1948 until their own in 2012. Although they mentioned their existence, some of those reports were not available in the databases used in this systematic review. Therefore, we could not include all of them in the quantitative and qualitative analysis.

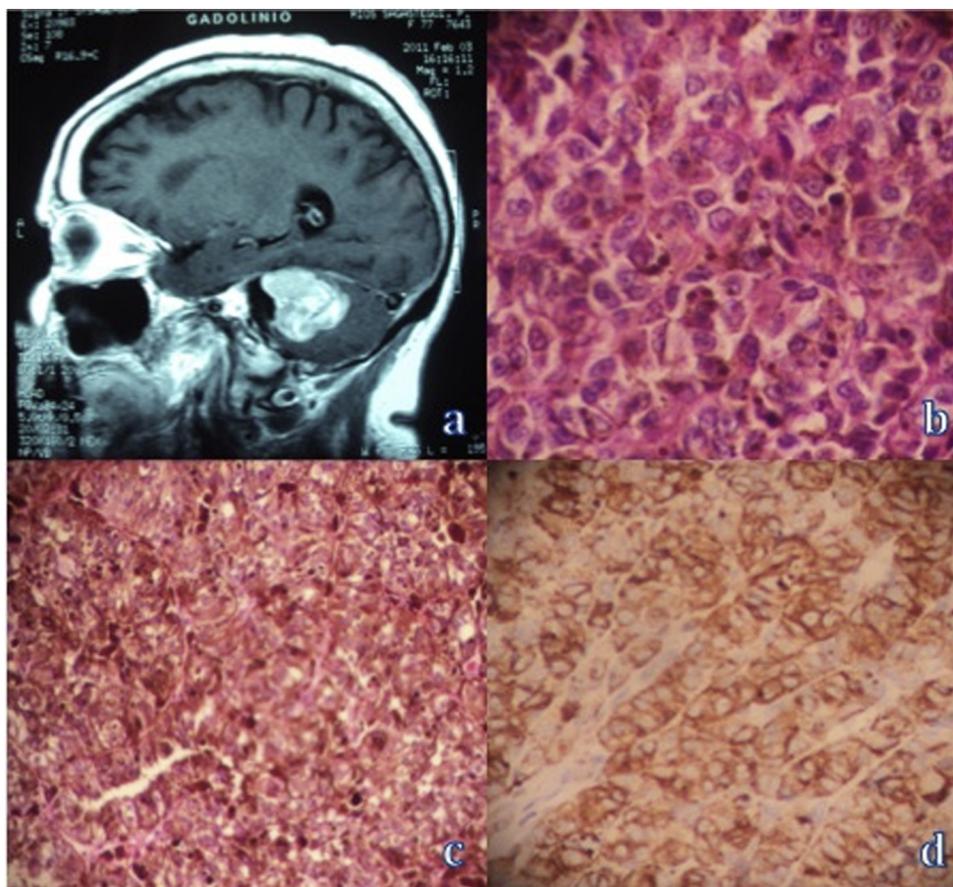


Fig. 2 – Case report images: contrast sagittal T₁-weighted MRI scan with a heterogeneous isointense lesion and hyperintense halo (a), hematoxylin and eosin staining demonstrating melanocytes containing pigment (b). Immunohistochemistry showing positivity with two melanocytic markers S-100 (c) and HMB45 (d) (magnification 40×).

The most frequent symptoms in the review were hearing loss, followed by ataxia and facial palsy. According to Block,²¹ CPA tumors are associated with specific neural symptoms according to the particular cranial nerve impairment. VII and VIII cranial nerves both pass through the CPA. Therefore, hearing loss and facial palsy are the two most frequent symptoms associated with CPA tumor, followed by cerebellar symptoms and hydrocephalus.^{22,23} Unilateral hearing loss, independently or together with tinnitus, affects the initial phase of CPA tumor. However, sudden deafness might be accompanied by vertigo, indicating an acute form of the disease and an aggressive nature of the tumor.^{24,25} Patients whose tumors grew rapidly (reported as high mitotic rate) had more acute symptoms. In the review, headache and vomiting were associated with an acute onset. Meanwhile, patients with impairment of the VII and VIII cranial nerves showed longstanding symptoms (months, even years), such as facial palsy, loss of taste, corneal reflex deficit, hearing loss and tinnitus. These results are similar to those presented by Lange et al.²⁶ on patients with CPA meningioma, who had frequent V, VII and VIII deficits, with cerebellar and increased intracranial pressure symptoms.

Pathology findings correlate with biological behavior.⁵ Malignant melanoma is characterized by large, atypical, pigmented cells; growing in nests or sheets; with bizarre,

pleomorphic, anaplastic nuclei; and high mitotic rates.²⁷ Melanoma can be confirmed by positive Masson Fontana stain, by negative epithelial membrane antigen or by immunopositivity for S100 protein and HMB45 and/or melan A.¹⁸ Mitotic rates more than or equal to 4/10 high-power fields (HPF) and MIB-1 labeling index more than or equal to 5% are usually present in high-grade melanoma, indicating rapid cell proliferation and poor prognosis.^{5,27}

Reports after 1990 used MRI as the gold-standard imaging method to assess PCPAM. The most common findings were hyperintense T₁- and T₂-weighted MRI; however, they were not consistent in all the reports (Table 1). The imaging characteristics of melanocytic lesions depend on the melanin content and hemorrhagic nature of the tumor. As the melanin content increases, there is more dipole–dipole interaction between melanin free radicals and water protons.⁷ Therefore, greater melanin content of the cells yields in hyperintense T₁- and T₂-weighted images.²⁸

The accuracy of the differential diagnosis is essential. Clinicians and surgeons might be advised to increase their efforts to find a melanoma extracranial origin, as the management and prognosis will differ significantly depending on where the tumor originated. Differential diagnosis for primary CPA tumors includes melanotic schwannoma, pigmented meningioma, metastatic melanoma and meningial

melanocytoma.¹ The first systematic differential diagnosis method distinguishing primary from metastatic melanoma of the CNS was reported by Hayward.²⁹ The criteria suggesting a primary CNS origin were: involvement of spinal or cranial leptomeninges; intramedullary spinal lesions; pineal or pituitary gland tumor; solitary brain lesion; hydrocephalus; and the exclusion of an evident melanoma outside the CNS (synchronous or metachronic).

Furthermore, Wadasadawala et al.⁷ proposed clinical features to distinguish between primary and metastatic melanoma of the CNS. Patients with metastatic lesions are prone to present at an age above 50 years old, with multiple lesions, almost always with extracranial disease, usually rapid clinical course, dismal prognosis and usually absence of neurocutaneous syndromes. In this review, the criteria for the diagnosis proposed by Hayward matched in all the cases. However, the clinical features proposed by Wadasadawala et al.⁷ were different across the reports.

Identification of the primary origin of the tumor is very important to consider for the treatment, as the choice of systemic versus local therapy depends on it. Positron emission tomography (PET), which uses fluorodeoxyglucose labeled with Fluorine-18 (FDG), is indicated for determining the origin of malignant melanoma.³⁰

There is no standardized treatment to manage PCPAM. Although treatments for metastatic brain melanoma include early diagnosis, surgery and radiotherapy and chemotherapy (temozolomide)³¹; primary CNS melanoma has been widely managed only with surgery, while the role and efficacy of radiotherapy and chemotherapy remains controversial.²⁷ According to Liubinas et al.,¹ total resection has a significantly better outcome than partial resection, with post-operative radiotherapy in all cases, when possible. Therefore, complete resection and radiotherapy are still the gold standard for the treatment of PCPAM.^{1,27}

All patients underwent neurosurgical treatment due to worsening of symptoms and mostly all received radiotherapy after surgery. Nevertheless, there was pronounced survival outcomes and prognosis inconsistency among the cases. The literature about the prognosis of PCPAM is scant and differs across the reports. For instance, Kan et al.¹⁵ reported poor survival rates for PCPAM: 13.6% of patients surviving less than a month, and 20% more than 12 months. Greco Crasto et al.³² reported survival outcomes of more than 5, 9 and 12 years. In this cohort of cases, almost half of the patients died within a year after the surgery, while the other half had longer than a year survival rates.

The variations in symptoms and prognosis across the reports cannot be explained with certainty. However, one attempt might be that the actual diagnosis was not a PCPAM, but metastatic, and clinicians failed to locate the primary focus. This might threaten the validity of the reports, which is not the intention of this review. Another reason for these variations is the diverse biological nature of these lesions, which correlates well with the prognosis of the tumor.

Currently, there is little information about genetic alterations explaining the causes of the different characteristics of these tumors. Melanoma genesis is related to alterations in the mitogen-activated protein kinase (MAPK) signaling pathway,

important for melanocyte homeostasis and survival. Different mutations lead to MAPK activation, and those from CNS differ from those of the skin.³³ GNAQ is a gene that encodes a protein that up-regulate the MAPK pathway,³⁴ and its mutation are preferentially present in a group of melanocytic lesions located in leptomeninges.^{35,36} Kusters-Vandeveldt et al.³⁶ and Gessi et al.³⁵ analyzed several cases of primary CNS melanocytic tumors and suggested that the presence of GNAQ mutation might favor a primary location in the CNS and a benign nature (i.e. melanocytoma); whereas GNA11 mutation (a GNAQ homologue) suggested an aggressive nature (i.e. PCPAM). Although it is difficult to associate this mutation to the aggressiveness behavior of certain primary CNS melanomas, literature suggests that genetic analysis help in the differential diagnosis and prognosis of this disease: GNA11 mutation seems to lead to a poorer prognosis than the GNAQ mutation.³⁵ Further investigation of molecular events underlying the diversity of these rare tumors will improve their management and prognosis with the use of inhibitors targeting GNAQ and GNA11 proteins.

The limitation for this systematic review was the small numbers of published cases in the literature. This difficulty led to make unfeasible the conduction of a meta-analysis of the data and to assess the results with caution.

6. Conclusion

1. The most frequent onset of symptoms was hearing loss, ataxia and facial palsy; its prompt identification leads to shorten diagnosis and improve prognosis.
2. The age of the patient and genetic nature of the melanoma are involved in the rate development and further spread of the tumor.
3. In clinical practice, because the management and prognosis differ significantly depending whether the tumor is primary or metastatic, surveillance of patients with CPA melanoma should be strengthened.
4. PET-scan with FDG and genetic analysis of GNAQ and GNA11 mutations play a new role in the seeking of the primary origin.
5. Nowadays, the gold standard treatment for primary CPA melanoma is still neurosurgical complete removal and adjunct radiotherapy.
6. Biological molecular differences between a primary and metastatic CPA melanoma might garner the attention of researchers in order to improve novel therapies.

Conflict of interest

None declared.

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