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Clinical outcomes of primary intracranial malignant melanoma and metastatic intracranial malignant melanoma

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ABSTRACT

Objectives: Primary intracranial malignant melanoma (PIMM) is extremely rare central nervous system (CNS) tumor and known for only composed 0.07% of the CNS tumors. PIMM composed only 1% of malignant melanoma and accordingly their clinical behavior and prognosis are not well documented. So, herein, we report our experience of pathologically proven PIMM, and compared their clinical characteristics and outcome with metastatic intracranial malignant melanoma (MIMM).

Patients and methods: Our institutional database was reviewed for patients who diagnosed as PIMM and MIMM pathologically between 1996–2016. As a result, a total of 6 patients of PIMM and 18 patients of MIMM were identified and analyzed. All these patients' clinical, radiological, histopathological and surgical records were obtained and reviewed.

Results: The median age of PIMM patients at initial surgery was 54.5 years (range, 30–60 years). During the mean follow-up of 12.8 months (range: 9–21 months), tumor recurrence occurred in 5 patients (83.3%). The overall survival rates of PIMM at 6, 9, 12 and 18 months were 100%, 83%, 50% and 25%. The PFS rates of PIMM at 3,6,9 and 12 months were 66.7%, 50%, 16.7% and 16.7%. The overall survival rates and progression-free survival rate difference between PIMM and MIMM were not statistically significant. ($p = 0.723$ and $p = 0.6$, respectively).

Conclusion: According to our experience, PIMM is very aggressive malignant tumor. Its median survival was less than 1 year. We suggest that maximal safe resection plus adjuvant RT and CTX for intracranial malignant melanoma considering highly aggressive clinical course of this tumors.

1. Introduction

Primary intracranial malignant melanoma (PIMM) is a very rare central nervous system (CNS) tumor. PIMM has been rarely reported in the literature and is found in only 0.07% of CNS tumors [1,2]. Non-CNS malignant melanoma is mostly cutaneous melanoma. Cutaneous melanoma is an aggressive malignant neoplasm that shows a very poor prognosis [3,4]. However, PIMM comprises only 1% of malignant melanoma cases, and accordingly, the tumor's clinical behavior and prognosis are not well documented. Because clinical information about PIMM is limited, preoperative diagnosis of PIMMs is difficult, and PIMM could be misdiagnosed as other disease entities such as other malignant brain tumors, metastatic brain tumors, and even benign tumors. The standard treatment strategy of PIMM has not been established. Moreover, the overall prognosis of PIMM is extremely poor. The overall reported survival of PIMM is 9–24 months [2,5]. In recent studies of intracranial melanomas, targeted therapy for mutated BRAF protein and immunotherapy that enhance the antitumor cell response have shown the survival benefit of metastatic malignant melanoma and leptomeningeal seeding [6,7]. To the best of our knowledge, there are several case reports of PIMM; however, there are few case series related to PIMM.

Here we report our experience of pathologically proven PIMM and compare the clinical characteristics and outcomes of PIMM with those of metastatic intracranial malignant melanoma (MIMM).

Abbreviations: CT, computed tomography; MRI, magnetic resonance image; PIMM, primary intracranial malignant melanoma; MIMM, metastatic intracranial malignant melanoma

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2. Patients and methods

This study was approved by our institutional review board, and all patients enrolled in this study agreed to publication in an academic journal. We searched our institutional database for patients histopathologically diagnosed with PIMM from 1996 through 2016. We defined PIMM as pathologically proven intracranial malignant melanoma with an unknown primary origin by detailed physical examination of the skin and eye as well as whole-body metastatic imaging work-up, including chest and abdomino–pelvic computed tomography (CT) scan and whole-body positron emission tomography (PET)–CT scan. We only included newly diagnosed cases of PIMM. To compare clinical outcomes, we also collected cases of surgically treated metastatic MIMM during the same period. We excluded patients with MIMM who underwent intracranial lesion treatment primarily by radiosurgery, radiotherapy (RT), and chemotherapy (CTX). We also excluded cases for which information was not available, cases that were diagnosed radiologically, and cases that were treated without surgery. In total, we identified and analyzed 6 patients with PIMM and 18 patients with MIMM. We obtained and reviewed the clinical, radiological, histopathological, and surgical records of all these patients.

The initial follow-up involved clinical evaluation and magnetic resonance imaging (MRI) at 1 month after surgery, followed by a checkup every 3 months.

We performed PIMM and MIMM group comparisons using the Mann–Whitney test and Fisher's exact test. We also investigated the overall survival (OS) and progression (or recurrence)-free survival (PFS) of our patients as well as prognostic factors. We defined the OS period as the time between the date of the initial diagnosis and the date of death and the PFS period as the time between the date of initial treatment and date of tumor recurrence or progression based on radiological findings. We analyzed OS and PFS using Kaplan–Meier survival analysis and the log rank test, prognostic factors using Cox proportional hazards models. We conducted all statistical analysis using SPSS ver. 18.0 (SPSS Inc., Chicago, IL) and considered p values < 0.05 as statistically significant.

3. Results

3.1. Clinical characteristics and radiological and histological findings of enrolled patients

Our present study cohort of cases with PIMM included 4 men (66.7%) and 2 women. The median age at initial surgery was 54.5 years (range, 30–60 years). The clinical manifestation varied: 2 patients (33.3%) visited the clinic with a headache, 2 with hemiparesis (33.3%), 1 with a change in the mental status (16.7%), and 1 with an incidental finding (16.7%). There were 18 patients with surgically treated MIMM [11 men (61.1%) and 7 women (39.9%)] in the MIMM series. The median age at brain lesion surgery was 48 years (range, 21–70 years). The clinical manifestation of MIMM also varied: headache was the most common clinical manifestation (n = 12, 66.7%), followed by hemiparesis (n = 2, 11.1%), dysarthria (n = 2, 11.1%), a change in the mental status (n = 1, 5.6%), and dizziness (n = 1, 5.6%). There was no statistical difference in basal characteristics between the PIMM and MIMM groups. Details of basal characteristics of patients with PIMM and MIMM are described in Table 1.

The location of PIMM was the supratentorial region in 5 patients (83.3%, total 6 patients) and the posterior fossa in 1 patient (16.7%). The mean tumor size was 46.3 mm (range, 25–72 mm). The most commonly affected area was the frontal lobe (n = 3, 50%), followed by the parietal lobe (n = 2, 33.3%). One patient had a tumor on the foramen magnum (extra-axial location). This patient was preoperatively misdiagnosed with foramen magnum meningioma. In case of MIMM, the most commonly affected area was the frontal lobe (n = 6, 33.3%), followed by the temporal lobe (n = 5, 27.8%), cerebellum (n = 5, 27.8%), and parietal lobe (n = 2, 11.1%). The tumor multiplicity of both PIMM and MIMM was 16.7% (1 and 3 patients, respectively).

Table 1
Basal characteristics of patients with primary intracranial melanoma (PIMM) and metastatic intracranial melanoma (MIMM).

		PIMM (n = 6)	MIMM (n = 18)	P value
Sex	M	4 (66.7%)	11 (61.1%)	p = 1.0
	F	2 (33.3%)	7 (39.9%)	
Age (years)	Mean	52 (38–60)	51.2 (21–70)	p = 0.923
	Median	54.5	48	
Presentation Symptoms	Incidental	1 (16.7%)	0	
	Headache	2 (33.3%)	12 (66.7%)	
	Mental change	1 (16.7%)	1 (5.6%)	
	Hemiparesis	2 (33.3%)	2 (11.1%)	
	Dysarthria	0	2 (11.1%)	
	Dizziness	0	1 (5.6%)	
Location	Frontal	3 (50%)	6 (33.3%)	
	Parietal	2 (33.3%)	2 (11.1%)	
	Temporal	0	5 (27.8%)	
	Occipital	0	0	
	Cerebellum	0	5 (27.8%)	
	Foramen magnum	1 (16.7%)	0	
	Intra-axial	5 (83.3%)	18 (100%)	
	Extra-axial	1 (16.7%)	0	
No. of tumor	Single	5 (83.8%)	15 (83.3%)	p = 0.712
	Multiple	1 (16.7%)	3 (16.7%)	
Size (Maximal Diameter)	Mean (mm)	46.33 (25–72)	44.77 (22–85)	p = 0.647
	≥ 50 mm	2 (33.3%)	3 (16.7%)	
	< 50 mm	4 (67.7%)	15 (83.3%)	
Type	Solid	1 (16.7%)	6 (33.3%)	p = 0.277
	Cystic	1 (16.7%)	5 (27.8%)	
	Hemorrhagic	4 (66.4%)	7 (38.9%)	
Molecular Marker	HMB-45	4/4 (100%)	14/15 (93.3%)	
	S100	3/3 (100%)	13/14 (92.8%)	
	BRAF V600E mutation	0/2	5/8 (625%)	

LM seeding, leptomeningeal seeding; HMB45, human melanoma black-45; BRAF, serine/threonine-protein kinase B-Raf.

On MRI, 66.7% (n = 4/6) of PIMM tumors showed a high signal intensity on T1-weighted images, 83.3% (n = 5/6) of PIMM tumors showed a low signal intensity on T2-weighted images, and 83.3% (n = 5/6) of tumors showed contrast enhancement on gadolinium (Gd)-enhanced T1-weighted images. Diffusion restriction degrees on diffusion-weighted images varied. We categorized 3 tumor types: only solid tumor, cystic tumor, and hemorrhagic tumor. Four of 6 patients (66.7%) with PIMM harbored hemorrhagic tumors and 1 patient harbored a cystic tumor. In the MIMM patient group, 7 patients (38.9%) harbored hemorrhagic tumors and 5 patients (27.8%) harbored cystic tumors. The incidence of hemorrhagic tumors was higher in patients with PIMM than in those with MIMM; however, the difference was not significant. Radiological features of PIMM and MIMM are described in Fig. 1.

Four of 6 patients with a preoperative radiological diagnosis of PIMM had malignant brain tumors, including high-grade glial tumors or metastatic brain tumors. However, 1 patient was diagnosed with meningioma and another with cavernous malformation in the preoperative period (Fig. 2).

Histopathological examination revealed melanin-pigmented large cells with bizarre nuclei, nuclear pleomorphism, and mitosis on both PIMM and MIMM (Fig. 3). Human melanoma black-45 (HMB-45) antibody and S-100 protein were positive in 4 of 4 patients (100%) and in 3 of 3 patients (100%) with PIMM, respectively. In the MIMM series,