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Intermediate-grade meningeal melanocytoma associated with nevus of Ota: a case report and review of the literature

Donghoon Shin, **Milind Sinha**, **Douglas S. Kondziolka**, **John M. Kirkwood**, **Uma N.M. Rao**, **Ahmad A. Tarhini**

University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Abstract

Meningeal melanocytomas are rare melanin-producing tumors that are often found to be benign. However, a small subset of these tumors can present as intermediate-grade melanocytomas (IGMs) that have histopathological features that are between those of benign melanocytomas and malignant melanomas. IGMs have the potential to recur and metastasize or progress to a more histologically high grade melanoma. Melanocytomas appear to differ from primary and metastatic melanoma by their prolonged clinical course and they appear to have different driver mutations (i.e. mutation of *GNAQ* gene). The association of a meningeal melanocytoma with nevus of Ota is extremely rare. To our knowledge, there have been only 10 reported cases of synchronous occurrence and only one of the cases involved an IGM. We report the second case of intermediate-grade meningeal melanocytoma that is associated with congenital nevus of Ota. Histopathological work-up confirmed the intermediate grade of the lesion and a driver *GNAQ*, mutation was identified consistent with previous reports.

Keywords

melanoma; meningeal melanocytoma; nevus of Ota

Introduction

Primary meningeal melanocytic tumor (PMMT) is a rare melanin producing tumor of the central nervous system (CNS). It originates from scattered, normally occurring melanocytes in the leptomeninges derived from migrated neural crest cells [1]. PMMTs are usually located in the leptomeninges adjacent to medulla oblongata and anterolateral spinal cord [2]. The oculodermal nevus of Ota is a hyperpigmented lesion that occurs in skin and mucosa innervated by the first and second branches of the trigeminal nerve, predominantly in Asian females [3]. Synchronous occurrence of melanocytoma and nevus of Ota is rare, with only 10 previously reported cases to our knowledge [1,4-12]. All except one case were associated with benign melanocytoma [7]. The current understanding indicates that melanocytoma and nevus of Ota have a common origin [12].

Correspondence to Ahmad A. Tarhini, MD, PhD, University of Pittsburgh Cancer Institute, UPMC Cancer Pavilion, 5150 Centre Avenue (555), Pittsburgh, PA 15232, USA, Tel: +1 412 648 6578; fax: +1 412 648 6579; tarhiniaa@upmc.edu.

Conflicts of interest

There are no conflicts of interest.

Reviews of a relatively small number of reported PMMTs that have prolonged follow-up including cases that have recurrences or metastases, has made it possible to estimate their potential biologic behavior using histomorphological parameters and proliferative activity of the constituent cells [5]. The spectrum of reported melanocytomas ranges from benign melanocytoma to cases behaving as overt melanoma with a small percentage (< 1%) categorized as intermediate grade depending on the proliferative activity determined either by mitotic activity observed on routine stains or with immunohistochemical stains (Ki-67/MIB) [13]. The intermediate-grade melanocytomas (IGMs) have the potential to recur and metastasize or progress to a more histologically high grade melanoma [10,14-16]. Nevus of Ota has also been reported to transform to melanoma and is associated with malignant melanocytic lesions [17-21]. Therefore, the management and the follow-up of affected patients has to be undertaken using this perspective.

Case report

A 56-year-old white woman was being worked up for thyroidectomy when she reported, headache, episodes of feeling confused, word finding difficulty, confusion lasting less than a minute and dysphagia in the previous 5–6 months. Her medical history included multinodular goiter and a right periorbital congenital nevus consistent with nevus of Ota. Her physical examination did not show any altered mental status nor abnormal cranial nerve function.

On imaging, brain MRI showed evidence of two midcranial fossa lesions, both in the left temporal area, measuring 4 and 1.8 cm. The larger lesion appeared to have acute intralesional hemorrhagic component that measured 3.3 cm, which was associated with vasogenic edematous change in the left temporal lobe with mild mass effect. The lesions were T2 isointense to hypointense on MRI and demonstrated avid contrast enhancement along with dural tails. A total body PET/computed tomographic scan showed no evidence of metastatic disease nor obvious primary malignancy.

The patient underwent a left frontotemporal craniotomy for microsurgical resection and dural biopsy. At the time of the surgery, melanotic black staining of the bone flap and the dura around the temporal and the sphenoidal wings were observed. The pathology (Figs 1 and 2) confirmed melanocytoma from both lesions and the dural biopsy. Heavily pigmented, spindled melanocytes growing in interlacing fascicles were noted. Immunostains were positive for S-100, HMB-45, Melan A and negative for epithelial membrane antigen and pankeratin. MIB-Ki-67 immunostains demonstrated proliferative indices of 2–3% in both lesions. Phosphohistone 3 confirmed the rarity of mitotic figures. Molecular genomic testing identified *GNAQ* mutation (p.Q209P, c.626A > C). No *BRAF, NRAS*, or *GNAS* mutations were identified.

Postoperatively, the patient developed left facial nerve palsy with limited movement of the lower hemiface and weak frontalis muscle. She also had diminished facial sensation in the ophthalmic distribution of the trigeminal nerve. The patient subsequently received stereotactic radiosurgery to the tumor bed that delivered a margin dose of 14 Gy and a maximum dose of 28 Gy. She was followed with repeat brain MRI, keeping in mind the

possibility of recurrence or progression to melanoma. After 2 years of follow-up, the patient has had no evidence of disease recurrence. MRI imaging continued to show no evidence of recurrent lesions nor abnormal enhancements.

Discussion

It is assumed that both PMMT and nevus of Ota have a common origin from the melanoblast of the neural crest. The melanocytes migrate in the 10th week of gestation widely to the cranial and the spinal leptomeninges, most abundantly ventral to the medulla oblongata but also in pons, cerebral peduncle and sylvian fissure. They are also present in other areas including the inner ear, skin and ocular structures [16]. In the case of nevus of Ota, the migration of melanocytes from the neural crest is arrested in the dermis rather than the dermoepidermal junction [22]. This abnormal migration of melanocytes can also variably present as cellular blue nevus, nevus of Ito, or Mongolian spots [22].

Nevus of Ota was first described by Hulke [23] in a patient with unilateral cutaneous hyperpigmentation with malignant melanoma of the sclera, and later in a case series in 1939 by Ota and Tanino [24] in 26 Japanese patients. About 60% are found at birth and 40% are found at puberty [25]. It is a congenital dermal hyperpigmentation syndrome that usually occurs in the first and the second division of the trigeminal nerve involving the eyelids sclera, conjunctiva, choroid, optic nerve and the adjacent skin [3]. Nevus of Ota is usually benign, but also appears to have a low malignant potential [17-21]. Clinically, it is seen in association with different types of vascular conditions like Takayasu's arteritis [26], vascular defect like Klippel–Trénaunay syndrome [27], cerebral malformation [28], Recklinghausen disease and others. Ballooning of posterior fossa producing a step like deformity of the occiput, facial hemiatrophy and pigmentation of the optic disc resulting in slower papillary light reflex have also been noted [5].

Meningeal melanocytoma was first described in 1972 by Limas and Tio [2]. In a review of the literature by Rahimi-Movaghar [5], 47.5% of melanocytomas were present in the intracranial region and 52.5% were found in the spine. Melanocytomas were more common in the supratentorial region and the thoracic region. They are associated with progressive neurological symptoms mostly due to mass effect, such as hydrocephalus, cranial nerve palsy, chronic spinal arachnoiditis, intracranial hemorrhage [29], psychiatric disturbance, myelopathy and radiculopathy [30]. Early reports of, melanocytomas described them as pigmented meningiomas, but they were found to lack the ultrastructural features of meningoepithelium, and contain melanosomes and pre-melanosomes in their cytoplasm [25]. Melanocytomas appear to differ from primary and metastatic melanoma by their prolonged clinical course and they also appear to have different driver mutations (i.e. mutation of *GNAQ* gene) [31]. The mean age of presentation with melanocytoma is in the fourth decade, and they occur more commonly in the female sex [5].

Imaging

The degree of melanin content causes variability in the appearance of melanocytoma on imaging studies. By computed tomographic scan, it is a well-defined, isodense/hyperdense lesion that strongly enhances after contrast [32]. It is often reported as meningioma if

it is not associated with nevus of Ota or if the reading radiologist is not aware of such an association [32]. MRI appearance depends on the paramagnetic effects of melanin. In our patient case, the lesions were T2 isointense to hypointense and showed avid contrast enhancement along with dural tails. This was consistent with other reported cases in the literature [32-34].

Pathology

Brat *et al*. [13], have classified meningeal melanocytic tumors into three categories ranging from benign meningeal melanocytoma to malignant melanoma with a small number of patients (< 1%) showing intermediate stage histological features. There have been case reports elucidating transformation from benign to a malignant histology [14,35,36]. The identification of tumor classification to low grade (melanocytoma), high grade (melanoma), and intermediate-grade lesions that bridge the two extremes is possible based on ultrastructural and immunohistochemical basis.

Benign meningeal melanocytoma is a pigmented and fairly well circumscribed lesion without evidence of local invasion [2]. It contains melanocytes that form compact and discrete nests, sheets or fascicles with more heavily pigmented cells at their periphery. This morphology has some similarity to the whorls of meningioma and is seen in melanoma and in IGMs [5]. They are well-differentiated with lower nuclear-to-cytoplasm ratio, and have small, regular, oval, or bean-shaped eosinophilic nucleoli [13]. Pleomorphism, necrosis, or hemorrhage is absent. Mitotic activity is less than 1/10 HPF and MIB-1/Ki-67 labeling index is less than 1–2% [13].

Indeterminate or intermediate differentiation category lesions have histopathologic features between those of melanocytomas and melanoma. They do not have the degree of hypercellularity, or anaplasia typical of melanoma and have low level mitotic activity (1–3/10 HPFs and MIB-Li of 1–4%) [13]. They also have sheet like pattern of growth, lack a nesting component and show microscopic CNS invasion [13]. The histologic features of these tumors thus overlap with those of hypercellular melanoma. The small number of intermediate lesions reported and the lack of complete and long-term followup make it difficult to draw conclusions regarding their behavior, but it appears that their recurrence rate and malignant potential are higher than those of benign melanocytomas [5].

Meningeal melanoma has the same anatomic distribution as melanocytoma and intermediate-grade tumors. It has variable histological and cytological appearance, including sheets and loose nests of spindled, epithelioid, and overtly anaplastic cells [13]. Significant amounts of melanin are present in tumor cells. Overt meningeal melanomas are hypercellular with increased nuclear-to-cytoplasmic ratios, and are more basophilic than melanocytomas and IGMs and cells have prominent nucleoli [13]. A small proportion of melanomas lack anaplasia or pleomorphism, but consists of fascicular or sheet-like proliferations of densely packed cells [13].

It is important to differentiate a melanocytoma from other pigmented tumors of the meninges, which include meningioma, melanoma and schwannoma. In contrast to meningioma, melanocytoma and melanoma stain positively for S-100, HMB-45, and Melan

A while staining negatively for epithelial membrane antigen and pankeratin [1]. The differentiation between melanoma and melanocytoma is based on hypercellularity, increased nuclear-to-cytoplasmic ratios, increased basophilia and features of aggressive behavior (CNS invasion, coagulative necrosis, increased mitotic activity of 3–6/10 HPFs, nuclear atypia, and MIB-Ki Li > 3–4%) [13]. Schwannomas stain positively for Leu7 and ultra-structurally, it has basal membrane and long spacing collagen [32]. Genomic mutation analysis (*BRAF, NRAS, HRAF*, and *GNAQ*) is also useful for differentiating between primary melanoma and metastatic melanoma [31]. Melanocytic lesions frequently have oncogenic mutations in signaling components of the MAP kinase pathway. Somatic activating mutations in codon 209 of *GNAQ* have been reported to be a frequent event in primary melanocytic lesions of the CNS [31]. Mutations of the *BRAF* gene have been reported to be found in ~40–50% of melanomas, while mutations in *NRAS* are present in ~20% [37,38]. Frequent somatic mutations of GNAQ have been reported in uveal melanoma [39].

The current case has a codon 209 GNAQ mutation and is consistent with an IGM based on the mitotic activity (2–3% Ki-67), histological features and the hemorrhagic component. Of PMMTs, the IGMs constitute a small percentage with only 13 previously reported cases [7,15, 40-50]. Furthermore, the association of PMMT with nevus of Ota is also rare. Interestingly, we found only one previous case report of IGM co-occurring with nevus of Ota and nine cases associated with benign melanocytoma [1,4-6,8-12]. The current case is, to our knowledge, the second reported case of IGM associated with nevus of Ota. A summary of previously reported cases of IGM and benign melanocytomas associated with nevus of Ota are presented in Tables 1 and 2.

Review of the 13 previously reported cases of IGMs shows that seven patients underwent complete surgical resection while six patients underwent partial resection [7,15,40-50]. Among those who underwent complete resection, one patient died within 7 days of presentation and four had local recurrence after at least 3 months of follow-up. Of those who underwent partial resection, four were reported to have tumor progression after at least 14 months of follow-up. Among 10 cases of benign melanocytoma associated with nevus of Ota, seven were alive after a follow-up varying from 6 months to 9 years [1,4-12].

Treatment

A previous review divided patients into three treatment subgroups that included tumor management with (a) complete surgical resection, (b) incomplete resection with radiotherapy, (c) incomplete resection without radiotherapy. In terms of recurrence rate, complete resection was superior to incomplete resection alone (20 vs. 82%, respectively) and incomplete resection with radiotherapy was superior to incomplete resection alone (15 vs. 82%, respectively) at 2 years of follow-up ($P < 0.05$) [48]. Although it was not statistically significant, a subsequent study showed a similar trend in deaths related to the disease in those with complete tumor resection or incomplete resection with radiotherapy compared with those with incomplete resection alone after 46 months of follow-up (5%, 6.7 vs. 23.5% respectively; $P>0.05$) [5]. Therefore, complete surgical resection when feasible followed by adjuvant radiotherapy appears to offer the best clinical outcome based on the current evidence.

Long-term follow-up of these patients is required since PMMT can recur and both PMMT and nevus of Ota have the potential for malignant transformation. The mitotic activity and labeling index could be useful predictors of the tumor behavior.

Finally, there are reports in the literature of cases of melanocytoma diagnosed in patients with a history of cutaneous and mucosal melanocytosis not consistent with nevus of Ota, supporting a close follow-up of such patients [51].

Conclusion

PMMT is a rare melanin producing tumor of the CNS that has been rarely reported in patients with nevus of Ota. To our knowledge, there are only 10 previously reported cases of synchronous occurrence and all except one case were associated with benign melanocytoma. The present case is the second reported case of synchronous occurrence of IGM and nevus of Ota.

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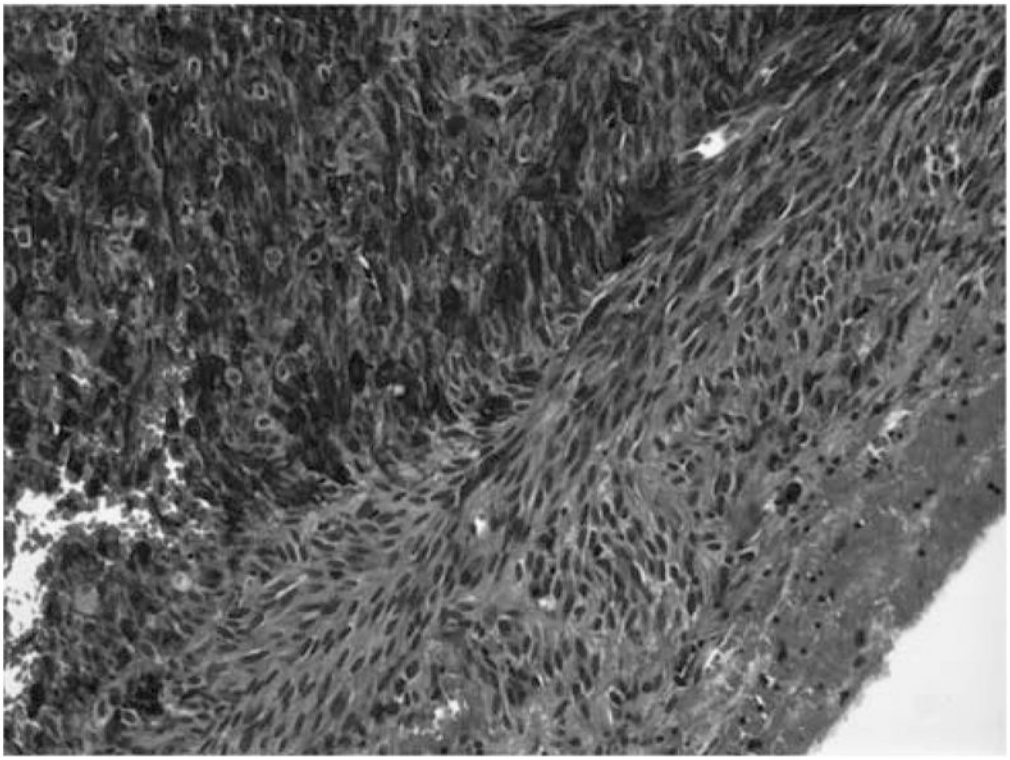

Fig. 1.

Dura with an adherent melanocytoma. A heavily pigmented neoplastic proliferation of spindled melanocytes growing in interlacing fascicles. Mitotic figures are only occasionally seen. Immunohistochemical stains were performed and demonstrated the tumor to be strongly immunoreactive for S-100, HMB-45 and Melan A (not shown) (hematoxylin and eosin, × 40).

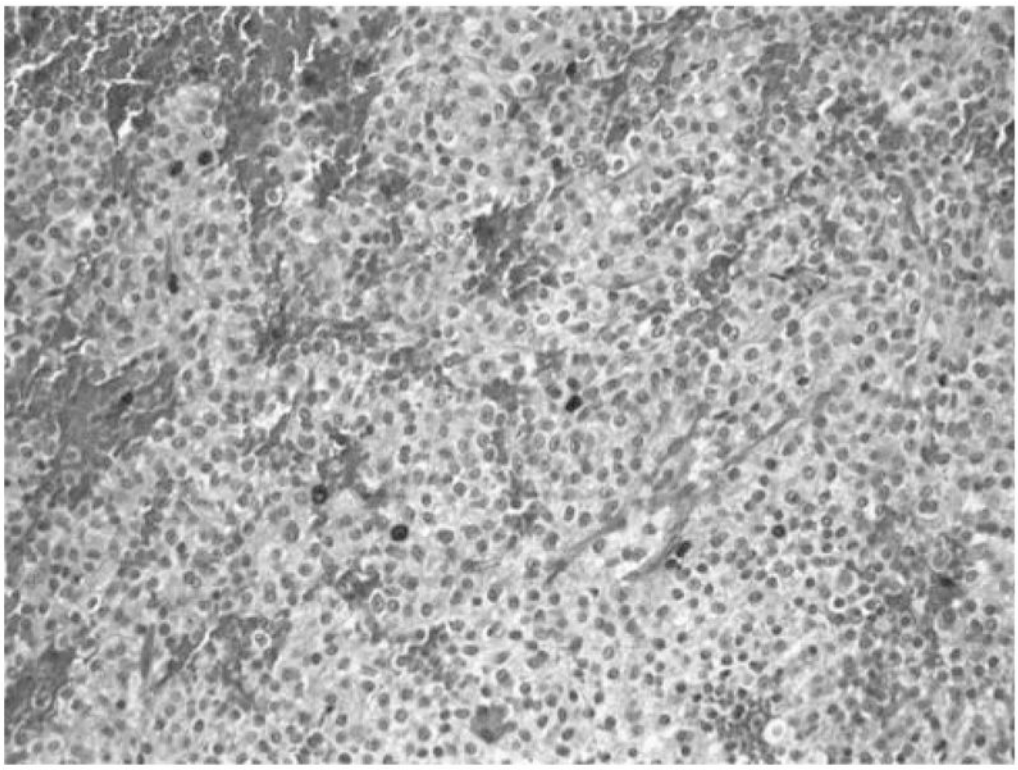

Fig. 2.

KI-67 immunostains demonstrate proliferative indices of 2–3% in the tumor. The KI-67 proliferation index is estimated as the percentage of positive tumor nuclei in the area of highest density and correlates with the paucity of mitotic figures observed.

Table 1

A summary of case reports of intermediate-grade meningeal melanocytomas

Case reference	Age	Sex	Nevus of Ota	Tumor grade	Initial therapy	Time to recurrence	Outcome/follow-up time	MIB-1/Ki-67 (%)
Delhaye *et al.* [50]	38	Female	No	IGM	TR	14 months	Deceased/4 years	10
El-Khashab *et al.* [41]	17	Female	No	IGM	PR	14 months	Alive/20 months	10
Gempt *et al.* [40]	71	Female	No	IGM	TR	3 months	Alive/1 8 months	2–12
Mangels *et al.* [44]	35	Female	No	IGM	PR+RT	None	Alive/20 months	1–2
Mathai *et al.* [43]	40	Male	No	IGM	TR	None	Alive/6 months	NA
Moser *et al.* [45]	34	Female	No	IGM	TR	8 months	Alive/8 months	10
Perrini *et al.* [15]	79	Female	No	IGM	PR	2 years	Alive/2.5 years	1–4
Rousseau *et al.* [46]	25	Female	No	IGM	PR	None	Alive/2 years	3
Uozumi *et al.* [49]	49	Male	No	IGM	TR	2 years	Deceased/5.5 years	0–40
Kini *et al.* [42]	35	Male	No	IGM[a]	TR	14 months	Alive/14 months	NA
Roser *et al.* [48]	37	Female	No	IGM[a]	PR	12 years	Deceased/14 years	3–25
Rades *et al.* [47]	23	Female	No	IGM[a]	PR	8 months	Deceased/4.5 years	NA
Navas *et al.* [7]	25	Male	Yes	IGM	TR	None	Deceased/7 days	8
This study	56	Female	Yes	IGM	TR + RT	None	Alive/2 years	2–3

Patient characteristics, tumor grade, presence of nevus of Ota, initial therapeutic approach along with recurrence and survival status are summarized.

IMG, intermediate-grade melanocytoma; NA, not available; PR, partial resection; RT, radiotherapy; TR, total resection.

[a]Initial presentation as benign melanocytoma that progressed/transformed to IGM.

Table 2

A summary of case reports of benign melanocytomas associated with nevus of Ota

Case reference	Age	Sex	Nevus of Ota	Tumor grade	Initial therapy	Time to recurrence	Outcome/follow-up time	MIB-1/Ki-67 (%)
Botticelle *et al.* [1]	43	Female	Yes	Benign	TR + RT	2 years	Alive/4 years	NA
O'Brien *et al.* [10]	13	Female	Yes	Benign	PR + RT	None	Alive/3.5 years	NA
Tregnago *et al.* [12]	28	Male	Yes	Benign	TR	None	Alive/7 months	NA
Moon *et al.* [9]	53	Male	Yes	Benign	TR	None	Alive/20 months	NA
Pan *et al.* [11]	36	Male	Yes	Benign	PR	None	Alive/1 year	< 10
Rahimi-Movaghar [5]	17	Male	Yes	Benign	TR	None	Alive/10 months	NA
Hino *et al.* [6]	75	Female	Yes	Benign	PR	None	Alive/2 years	0.40
Rutten *et al.* [8]	37	Female	Yes	Benign	TR	5 years	Alive/6.5 years	5
Piercecchi-Marti *et al.* [4]	25	Male	Yes	Benign	TR	None	Alive/4 years	NA

NA, not available; PR, partial resection; RT, radiotherapy; TR, total resection.