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Animal-type malignant melanoma associated with nevus of Ota in the orbit of a Japanese woman: a case report

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We present a patient with an animal-type malignant melanoma associated with the nevus of Ota in the orbit who showed a good prognosis after a combination of orbital extirpation, chemotherapy, stereotactic radiotherapy, and gamma knife. A 42-year-old Japanese woman presented with two tumors, one pathologically diagnosed as right-sided intraconal animal-type malignant melanoma and the other intracranially, presumed to be of the same pathogenesis and both were considered to have arisen from the nevus of Ota. She underwent an extirpation of the orbit, chemotherapy (DAV therapy, which is a combination of dacarbazine, nimustine, and vincristine), stereotactic radiotherapy (54 Gy in 27 fractions), and gamma knife (marginal dose was 17 Gy, target volume was 0.2 ml). She has been alive for 33 months since the extirpation, with no sign of local recurrence, new metastasis, nor enlargement of the intracranial tumor. Not just combination therapy but also the low malignancy of animal-type melanoma may have contributed toward the good prognosis. *Melanoma Res* 24:286–289 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The nevus of Ota is a light bluish nevus on the unilateral face, which is congenital or acquired in adolescents, and often seen in Asian females. Malignant transformations are rarely observed in the orbit [1] and seldom seen among Asians [2]. As the potential for local invasion or metastasis varies widely, strict prognostic indicators for orbital melanoma have yet to be established [3]. Animal-type melanoma is a rare type of malignant melanoma that usually arises in skin lesions [4] and shows indolent progression and good prognosis despite metastasis. To the best of our knowledge, this is the first case report of a primary animal-type malignant melanoma in the orbit that developed from the nevus of Ota to show a satisfactory clinical course.

Case presentation

A 42-year-old woman presented with a right-sided eye swelling and fever. She had suffered for 2 months before she presented to our department. She had been diagnosed with diabetes mellitus 2 years previously, but had received no medication. She had no particular family history, except for the fact that her father had stomach cancer. Bluish pigmentations were visible on her right forehead, ear, and eyelid since birth. Physical examination indicated black pigmentation in her right conjunctiva, tarsal plate (Fig. 1a), and palate. Visual acuity was 1.2/1.2 in each eye. Hertel exophthalmometry showed exophthalmos in her right eye [24 and 18 mm in the right and left eyes, respectively, with a base of 110 mm (Fig. 1a)]. Ocular movement of her right eye was restricted in both the horizontal and the upward gaze. Intraocular pressure was 19 mmHg in her right eye and 18 mmHg in her left eye. Fundus examination led to suspicion that there was hypoplasia of the right papilla. MRI showed a right-sided exophthalmos and a 2.5×3 cm large, well-defined intraconal mass. The tumor was heterogeneous and there was a slightly high intensity observed in the gadolinium-enhanced T1-weighted image (T1-WI) and a low intensity in the gadolinium-enhanced T2-weighted image (T2-WI) (Fig. 1b–d). The results confirmed that there was no enlargement of the rectus muscles. Another 5×6 mm large mass that was discontinuous with the orbital tumor in the cranial base was also observed and primarily presumed to be a meningioma (Fig. 1d). Laboratory tests indicated that her diabetes mellitus was uncontrolled (HbA1c, 11.5%) and that she had a normal LDH level (220 U/l). She also had hypertension.

Right-sided anterior orbitotomy and intraorbital tumor excision were performed. The tumor, which ruptured during the operation because of biopsy for pathological diagnosis, was frozen for later analysis. The tumor was a black, thin-walled capsule (Fig. 2a). Because the subsequent pathological diagnosis of the frozen specimen during the operation showed it to be a benign lesion, we completed tumor excision without orbital extirpation.

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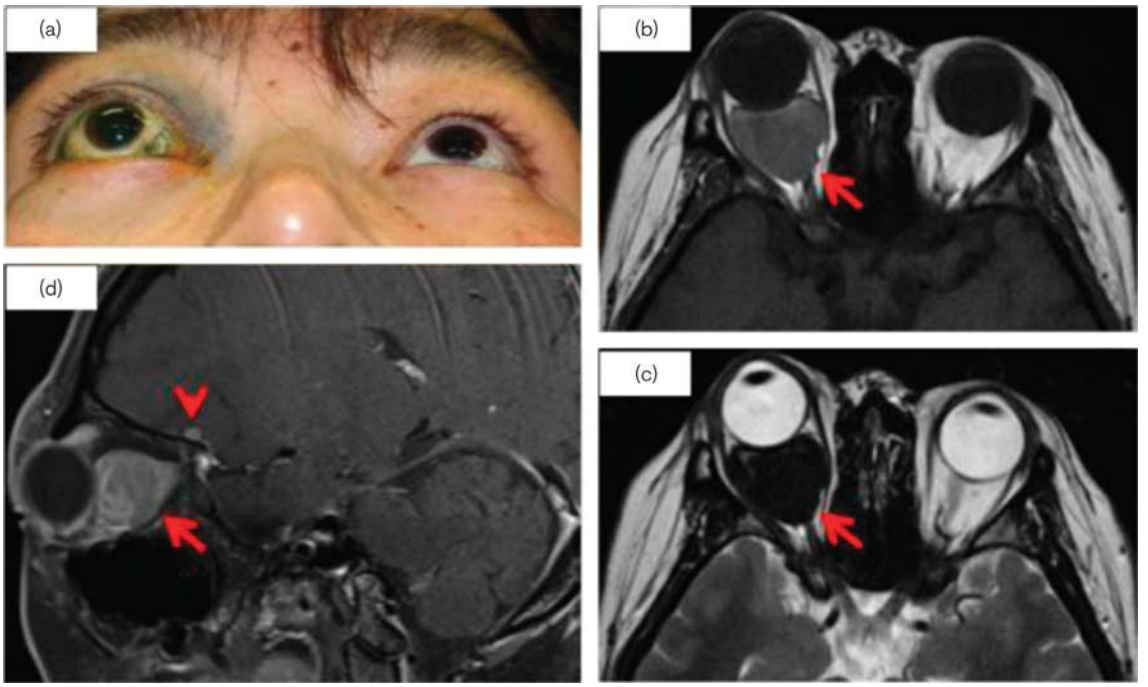
Fig. 1



(a) Bluish pigmentation was seen on the right eyelid and black pigmentation was seen in the right conjunctiva. Exophthalmos in the right eye was obvious. (b) T1-weighted image: right-sided exophthalmos was seen and the retrobulbar mass showed a slightly high intensity in the T1-weighted image (indicated by an arrow). (c) T2-weighted image: right-sided exophthalmos was seen and the retrobulbar mass showed low intensity in the T2-weighted image (indicated by an arrow). (d) Gadolinium-enhanced T1-weighted image. The retrobulbar mass was enhanced by gadolinium (indicated by an arrow). A 5 × 6 mm large mass, which was discontinuous with the orbital tumor in the cranial base, was also enhanced (indicated by an arrowhead).

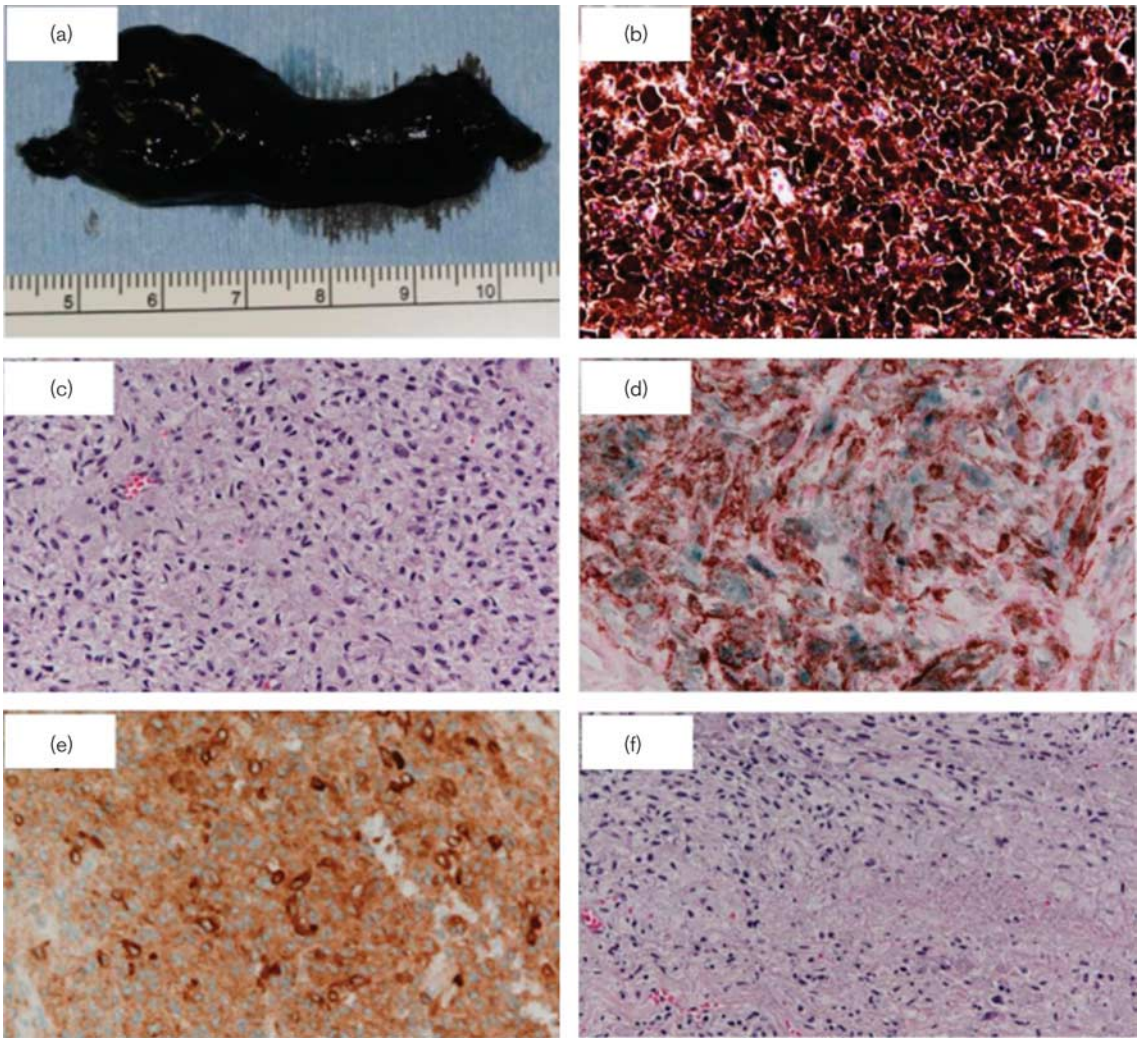
After preparation of the sample, the pathological examination of the tumor showed that the lesion was an animal-type malignant melanoma. The specimen was highly pigmented with melanin (Fig. 2b). After using a bleaching method for melanins, hematoxylin and eosin staining was performed (Fig. 2c). Diffuse proliferation of epithelioid cells and spindle cells was observed. All the cells had low-grade pleomorphic nuclei, with nucleoli observed in some cells, although they were not found to be prominent. HMB (Human Melanoma Black)-45 (Fig. 2d) and Melan-A (Fig. 2e) stainings, which are specific for melanocytes, were both positive. Geographic necrosis was observed in the parenchyma (Fig. 2f). Mitotic figures were not present.

We performed orbital extirpation with an excision of a 5 mm margin from the nevus of Ota; the orbit was then covered with a skin graft taken from the patient's thigh.

The pathological study showed the presence of widely spread pigmented nevus cells. These cells were found in the skin, subcutaneous fat, orbital muscle, orbital fat, lacrimal gland, and sclera. Results also showed that the retina, the uvea, and the cornea were not involved. Some parts of the nevus were cellular, with slightly large, round epithelioid melanocytes that contained low-grade pleomorphic nuclei. Although some of these were accompanied by small nucleoli, neither necrosis nor mitosis was observed. Clinically, this was considered to be nevus of Ota. Although no malignant changes were apparent at the time of the procedure, the findings did suggest the possibility that these atypical melanocytes might be an early stage of melanoma.

MRI performed before the second operation showed that there was a slight enlargement and high intensity in the T1-WI of the cerebral mass that had been considered as a meningioma before. This led to suspicion of metastasis to the brain. In addition to the second surgery, chemotherapy (DAV therapy, which is a combination of dacarbazine, nimustine, and vincristine), stereotactic radiotherapy (54 Gy in 27 fractions), and gamma knife (the marginal dose was 17 Gy and the target volume was 0.2 ml) were administered. Since then, we have examined her once every 2–3 months by laboratory tests including lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase. We have also taken some biopsies to check the orbital local recurrence and performed annual 18F-fluorodeoxyglucose positron emission tomography to check metastasis. Brain surgeons have checked the remaining brain tumor with regular MRI. Otolaryngologists and dentists have checked the pigmentation of the mouth

Fig. 2



(a) Macroscopy of the extracted orbital tumor: highly pigmented 6 × 2 cm large tumor, which ruptured during the extirpation. (b) Hematoxylin and eosin staining of the orbital tumor (× 20): melanin-containing cells (melanocytes and melanophages) are abundant in the tumor. (c) Hematoxylin and eosin staining of the orbital tumor after using a bleaching method for melanins (× 20): diffuse proliferation of the epithelioid cells and spindle cells, and low-grade nuclear atypia were seen. Small nucleoli were seen in some areas of the tissue. (d) HMB (Human Melanoma Black)-45 staining (× 20): positive for atypical cells. (e) Melan-A staining (× 20): positive for atypical cells. (f) Hematoxylin and eosin staining of the orbital tumor after using a bleaching method for melanins (× 20): vast areas of necrosis were seen.

and physicians have brought her severe diabetes mellitus under control. Thirty-three months have passed since the second surgery, with no sign of local recurrence, new metastasis, nor enlargement of the intracranial tumor.

Discussion

The nevus of Ota (oculodermal melanocytosis, naevus fusculocoeruleus ophthalmomaxillaris) was described by the Japanese dermatologist, Ota, in 1939. It is a light bluish nevus on the unilateral face, which is congenital or acquired in adolescents. It has been shown to be more common in East Asians (0.2–1.0%) than in western populations (0.04%) [5]. The incidence of malignant change is 0.5% for East Asians and about 25% for western populations [2]. Therefore, the calculated incidence of malignant melanoma associated with the nevus of Ota is 0.001–0.005% (0.2–1.0% × 0.5%) among East Asians, whereas it is 0.01% (0.04 × 25%) among western populations. Malignant melanoma associated with nevus of Ota has been reported to occur in the uveal tract [6], optic nerve head [7], brain, and orbit. As for western populations, Rice and Brown [8] reported finding six cases of primary orbital melanoma associated with nevus of Ota, whereas two other studies have additionally reported two more cases [1,9]. However, in terms of East Asian populations, ours is the first report of such a case.

The original report of the animal-type melanoma was based on a highly pigmented malignant melanoma that

was found in a horse and then shown to be a very rare variant of melanoma. It has been reported that this melanoma usually occurs in skin lesions found on the scalp, face, and extremities [10]. Of the eight reported orbital melanoma cases, pathological diagnosis indicated that five were spindle, two were epithelioid, and one was mixed [1,8,9]. The current patient is the first case of the animal-type melanoma that arose in the orbit.

Histopathologically, animal-type melanoma cells show some nuclear atypia and regular oval to round nuclear shapes, with moderate anisonucleosis, small nucleoli, and distributed chromatin. Characteristically, these do not fulfill the cytologic criteria of malignancy. The most important clue to the diagnosis of animal-type melanoma is effacement of the dermal architecture by areas of confluent melanocytic growth. Mitotic activity is usually very low [11]. In our case, all the cells had low-grade pleomorphic nuclei, with nucleoli seen in some cells. Mitotic figures were not present. Most importantly, the specimen was highly pigmented with melanin. These agree with the characteristics of animal-type malignant melanoma.

Distant metastases of animal-type melanoma are rare and even when they occur, these patients appear to have a better prognosis than those with an ordinary melanoma presenting with metastatic disease [10]. It may because of this characteristic that our patient showed neither enlargement of tumor nor neurologic symptoms for long despite an intracranial metastasis. However, even with this low malignant potential, animal-type melanoma is clearly a variant of melanoma [10]. Therefore, application of the guidelines used for melanoma, clinical investigation of regional and distant metastases, and surgical treatments with safety margins [12] are recommended in these types of cases [13]. Accordingly, we administered extirpation, chemotherapy, stereotactic radiotherapy, and gamma knife. Thirty-three months since the extirpation, the patient is still alive, with careful follow-up examinations, despite having intracranial metastasis. Not just the combination therapy but also the low malignancy of animal-type melanoma may have contributed toward this good prognosis.

Although the possibility is not high that malignant transformation occurs in the nevus of Ota, it is important to consider this possibility as it can be seen in any population groups. Doctors involved in the treatment of nevus of Ota (as in our case, ophthalmologists, pathologists, dermatologists, brain surgeons, otolaryngologists, radiologists, and dentists) should understand that malignant transformation could occur and should cooperate with one another for its treatment. Although practical strict prognostic indicators for orbital melanoma are yet to be established [3], this particular case suggests that the characteristic indolent progression of the animal-type melanoma might partly contribute toward the good prognosis.

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Conflicts of interest

There are no conflicts of interest.

References

1 John H, Britto JA. Nonchoroidal intraorbital malignant melanoma arising from naevus of Ota. *J Plast Reconstr Aesthet Surg* 2010; **63**:e387–e389.
2 Dutton JJ, Anderson RL, Schelper RL, Purcell JJ, Tse DT. Orbital malignant melanoma and oculodermal melanocytosis: report of two cases and review of the literature. *Ophthalmology* 1984; **91**:497–507.
3 Mandeville JT, Grove AS Jr, Dadras SS, Zembowicz AM. Primary orbital melanoma associated with an occult episcleral nevus. *Arch Ophthalmol* 2004; **122**:287–290.
4 Ludgate MW, Fullen DR, Lee J, Rees R, Sabel MS, Wong SL, *et al.* Animal-type melanoma: a clinical and histopathological study of 22 cases from a single institution. *Br J Dermatol* 2010; **162**:129–136.
5 Chen YC, Chang CH, Hsu SL, Hsu MW, Lee CL. Malignant melanoma of the choroid in the eye with oculodermal melanocytosis of a Chinese woman. *Kaohsiung J Med Sci* 2010; **26**:673–678.
6 Shaffer D, Walker K, Weiss GR. Malignant melanoma in a Hispanic male with nevus of Ota. *Dermatology* 1992; **185**:146–150.
7 Unal M, Gunalp I, Deery A, Durak I, Erekul S, Bulay O. Malignant melanoma of the optic nerve head in a case of oculodermal melanocytosis. *Br J Ophthalmol* 1992; **76**:313–315.
8 Rice CD, Brown HH. Primary orbital melanoma associated with orbital melanocytosis. *Arch Ophthalmol* 1990; **108**:1130–1134.
9 Koranyi K, Slowik F, Hajda M, Banfalvi T. Primary orbital melanoma associated with oculodermal melanocytosis. *Orbit* 2000; **19**:21–30.
10 Antony FC, Sanclemente G, Shaikh H, Trelles AS, Calonje E. Pigment synthesizing melanoma (so-called animal type melanoma): a clinicopathological study of 14 cases of a poorly known distinctive variant of melanoma. *Histopathology* 2006; **48**:754–762.
11 Magro CM, Crowson AN, Mihm MC. Unusual variants of malignant melanoma. *Mod Pathol* 2006; **19 (Suppl 2)**:S41–S70.
12 Tellada M, Specht CS, McLean IW, Grossniklaus HE, Zimmerman LE. Primary orbital melanomas. *Ophthalmology* 1996; **103**:929–932.
13 Bagny K, Anyfantakis V, Levillain P, Huguier V, Wierzbicka-Hainaut E, Guillet G. Animal-type melanoma with regional lymph node metastasis after a 5-year follow-up. *Int J Dermatol* 2013; **52**:90–92.