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RESEARCH ARTICLE

Ota Nevus of Skin, Eye and Orbit: Neglected Potential Risk of Developing an Orbital Melanoma, Even in Young Patients

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Abstract

Purpose: To demonstrate the presence of orbital pigmentation in a congenital nevus of Ota. Every medical practitioner should be aware of the increased risk of orbital melanoma.

Methods: Observational case report and review of the literature.

Results: A Caucasian man of 54 years was referred with blurred vision and skin melanocytosis in the dermatome of the ophthalmic- and maxillary nerve, also involving sclera, conjunctiva, iris and choroid. A large uveal melanoma was detected and an enucleation was indicated. During surgery melanosis of the orbital soft tissues and muscles was found. Only few reports in the literature describe orbital melanocytosis.

Conclusion: In the nevus of Ota, besides ocular melanosis, also orbital tissues may be involved, with a potential risk of developing an orbital melanoma. In patients with Ota not only fundoscopy, but also exophthalmometry and orbital imaging should be performed regularly.

Keywords: Oculodermal melanocytosis, ocular and orbital melanocytosis, melanosis, nevus of Ota, blue nevus, uveal melanoma, orbital melanoma.

1. Introduction

Ota nevus, also referred to as oculo-dermal melanocytosis, consists of abnormal deep tissue pigmentation in the territory of the trigeminal nerve and is associated with an increased risk of developing choroidal melanoma (1). From a pathological view Tellado et al (2) revealed an important role of orbital melanocytosis in the development of primary orbital melanomas. They analyzed 21 orbital melanomas of which 19 had a blue nevus or melanocytosis. At least 13 other case reports of an orbital melanoma in patients with Nevus of Ota have been reported.

We found only 6 reports describing the involvement of the orbital tissues in Ota nevus and only 2 papers show an image of the pigment present on the periorbita or the orbital fat.

We present a patient with an Ota Nevus who developed a choroidal melanoma and was treated by enucleation. During the surgery pigmentation of the orbital soft tissues and extraocular muscles was found. Pictures are shown.

We will discuss the characteristics of Ota nevi and explain the origin of the pigment distribution, in order to understand why orbital melanoma can arise and why orbital examination in every patient with oculodermal melanocytosis is important. Since these patients often reach the ophthalmologist when the melanoma is already large, it is important that all medical doctors should be aware of this potentially lethal risk and notify the patient of the necessity of regular ophthalmic and orbital screening.

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2. METHODS

Case report describing preoperative discovery of pigmented cells in the orbit in a patient with OTA, and review of the literature.

3. RESULTS

3.1 Case Report

A 54-year-old Caucasian man presented with vision decrease in the left eye associated with photopsia. He had ocular and periocular pigmentation on the left side, since birth (fig 1). On examination, hyper pigmented dark grey blue skin was found in the distribution of the left trigeminal region V 1 and V2. No increased pigmentation was noted in the territory of the V3 or palate. Sclera, conjunctiva, limbus, trabeculum and iris of the left eye were also hyper pigmented (Fig 2). The right eye was normal. Visual acuity was 1.0 in the right eye and 0.4 in the left eye.

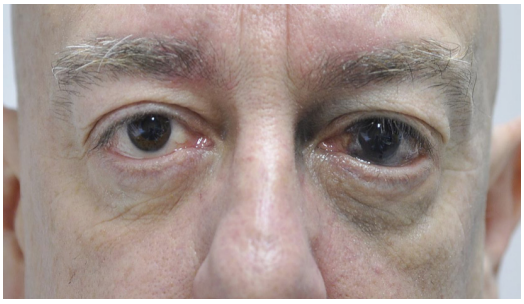

Figure 1. *Periocular deep pigmentation of the left V1 and V2 territory, normal pigmentation on the right side*

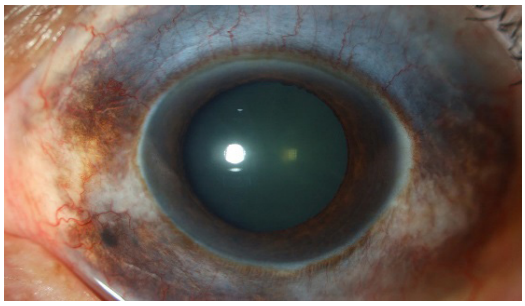

Figure 2. *Hyperpigmentation of sclera, conjunctiva, limbus and iris of the left eye*

A big pigmented mushroom shaped mass was found on fundoscopy in the left eye. (fig. 3) The tumor measured: 9 thickness and base of 13 x12 mm and was located around the optic disc. No extraocular extension was found on ultrasound and magnetic resonance imaging (MRI).

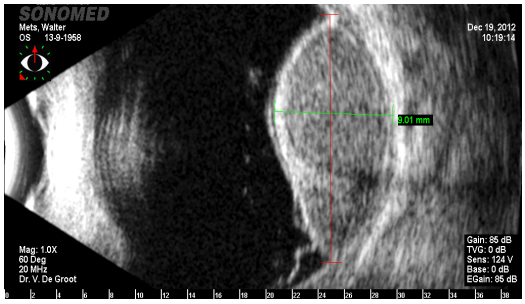

Figure 3. *Choroidal melanoma of the left eye (this figure could be deleted)*

A diagnosis of choroidal melanoma was made, and the eye was enucleated. During surgery deep pigmentation of the extraocular muscles (superior, lateral and medial rectus) and orbital fat was found (fig. 4, 5). The eye was removed with as much extraocular pigment as possible and an orbital implant was placed in the cavity.

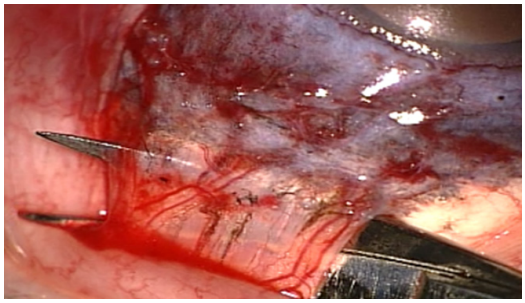

Figure 4. *Extraocular rectus muscle with pigmentation along its fibers. Picture taken during enucleation.*

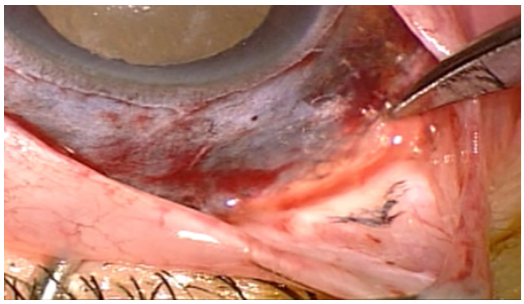

Figure 5. Melanosis on the inside of tenon's capsule.

Pathological analysis of the tumor confirmed the diagnosis of malignant choroidal melanoma without trans scleral extension and no invasion in the optic nerve. The tumor consisted of spindle shaped cells containing melanin in whorl formation. Other ocular tissues, as tenon, trabeculum, intrascleral vessels, irisstroma, corpus ciliare and uvea, demonstrated excessive pigmentation (Fig 6). Pathological analysis of melanosis at orbital Tenon capsule and rectus muscle demonstrated melanin deposits in connective and fat tissue with a few melanocytes with slight nuclear atypia (Fig 7). Four years after enucleation, the patient was diagnosed with liver metastasis, leading to death.

3.2 Review of Reported Cases with Melanosis of the Orbit

In a literature review of all primary orbital melanomas we only found 9 papers describing the presence of orbital pigmentation during surgical exploration and only 2 show a picture of the orbital melanosis. In 7 of them ocular or oculodermal melanocytosis was described.

Rottino (3) describes a slowly growing tarry black mass completely filling the orbit, with inside a firm gray non-pigmented melanoma. The pigmented mass was composed largely of melanin, free and intracellular, arranged in large dense masses infiltrating fatty, loose tissue and epineurium of various nerve trunks, extending through the optic foramen to the brain were it was incompletely removed. After adjuvant radium treatments, he had at least no recurrence or distant metastasis up to one year.

Hagler (4) presents a man with a congenital Ota nevus of left upper and lower lid and conjunctiva, who had a 3-year history of progressive proptosis, revealing a massive malignant melanoma in the apex of the orbit. During exenteration pigmentation of the periosteum and the bony orbital floor was seen. The orbital tissues showed a wide variation in the histology of the scattered pigmented strand like lesions. From spindle-shaped dendritic cells with no mitotic figures, and masses resembling cellular blue nevus, to larges sheets of minimally pigmented pleomorphic cells of the malignant melanoma.

Haim (5) described the removal of a large non-encapsulated melanoma of fragile consistency. The tumor contained large polygonal anaplastic cells with moderate number of mitotic figures. He found a large black pigmentation of the orbital bone, the periosteum and orbital fat (with photograph).

Koca (6) published a case of spindle cell melanoma. During tumor resection they discovered benign melanocytosis of the dura, optic nerve, orbital fat and bone. Pathology demonstrated benign polymorph spindle shaped melanocytes near the dura, with mitoses figures, prominent nuclei and cell atypia.

Koranyi (7) presented a primary orbital melanoma in a patient with bony asymmetry and a larger orbital volume at the tumor side. The black tumor with fragile ruptured capsule contained spindle shaped cells arranged in whorls or showing a streaming pattern. Pathology revealed a more benign type of melanoma with very few mitoses, and he concluded that there must have been a slow progressive form of melanosis. Surrounding orbital tissue, lateral rectus muscle and the posterior wall of the bony orbit showed extensive black pigmentation. The patient had interferon alpha-2b for two years without any signs of recurrence after 3-year follow-up.

Wilkes (8) describes a para bulbar encapsulated melanoma in a 18 year old black man with ocular melanocytosis. Orbital connective tissue in the exenteration specimen showed multiple complex patterns of melanocytes of various shapes, sizes and degrees of atypia. Most conspicuous were nodules of pigment-laden, spindle-shaped, and dendriform cells resembling those seen in cellular blue nevus.

Rice (9) presented a case of primary orbital encapsulated melanoma in a pregnant woman without any superficial pigmentation. Pathology revealed densely packed pleomorphic spindle cells with few mitotic figures. During surgical removal focal areas of pigmentation remote from the main tumor were visible along the periorbita (with photograph), a

histologically confirmed bleu nevus with heavily pigmented dendritic melanocytes. A nerve within the melanoma demonstrated identical pigmented dendritic cells infiltrating the perineural sheath.

Dutton (10) describes a 15 year old boy with oculodermal melanocytosis in which an orbital melanoma was removed, and clumps of pigment were found in the dermis of the eyelid and throughout the orbit. A few months later numerous elevated skin nodules and a mass in the superior orbit was found. During surgical biopsy more diffuse pigment with clumps were encountered throughout to the orbital fat and extraocular muscles, the scalp, periosteum, the outer tabula of the frontal bone and dura mater. Histology showed nests and fascicles of plump spindle-shaped cells having uniform nuclei without nucleoli or mitotic figures. Coarse brown pigment granules were deposited along the margin f collagen fibers.

Ranjit (11) describes an old woman with primary orbital melanoma in the apex, with pigmentation in the adjacent soft tissue and metastatic melanoma in the optic nerve itself without pigmentation of the nerve sheath. Dickens et al (12) describe a patient with an episleral orbital melanoma, with separate pigmentation in adjacent tissue, confirmed by pathological examination of melanosis of a bleu naevus.

4. Discussion

4.1 Ota Nevus

The nevus of Ota (naevus fusculocoeruleus ophthalmomaxillaris) was first described by the Japanese dermatologist M.Ota in 1939 (13). The characteristics of Ota nevi are deep, usually flat blue grey skin pigmentation in the distribution of the ophthalmic, maxillary and, more rarely, mandibular divisions of the trigeminal nerve (1, 14-16). Mostly unilateral, although bilateral cases have been described (17). The sex ratio is 2 to 4,8 woman for 1 man (1, 15, 16). Whether detection might be enhanced in woman because of esthetic complaints is unknown. Ota nevi are more often seen in the Asian and Black population, and are less frequent in Caucasians. In the white population, the prevalence of ocular melanocytosis was determined to be 0.038% (18). The onset of the disease has a peak at birth and adolescence, possibly already present at birth with increased pigmentation due to hormonal changes.

The melanocytosis is caused by spindled, bipolar or dendritic melanocytes occupying the skin, soft tissue, uvea, episclera, oral and nasal mucosae, but also the external auditory canal, tympanic membrane, orbital tissue, meninges and brain can be involved (16, 19). Table 1 shows the sites of pigmentation documented in two large studies (1, 15). Two types of melanosis can be distinguished. The ocular melanosis is located in the deep episclera and sclera, and in the uveal tract. The dermal melanosis is located in the periocular skin, often also involving the conjunctiva, orbit and meningae (type of ITO) (1, 20, 21). The nevus of Ota is the combination of both types, also referred to as oculodermal melanocytosis (1).

4.2 Origin of Melanocytosis

After gastrulation (when ectoderm, mesoderm and endoderm differentiate), the neural crest appears at the border of the neural plate and the non neural ectoderm. The neural crest cells are multipotent cells that under influence of various factors migrate to form a wide range of tissues. Round 20 days, the mesencephalic neural crest is visible. This cranial part of the neural crest will give cells for many tissues such as tendons of extraocular muscles and connective tissue of the orbit. Both early and late migrating neural crest cells give melanocytes. The late migrating neural crest cells give rise to dorsal root ganglion neurons as well as melanocytes (22, 23). They migrate along the oculomotor and trigeminal nerve, but they are never found in the mandibular arch. This could explain why involvement of the region of the mandibular branch of the trigeminal nerve is so rare in Ota nevus. Under still unknown influence, the melanocytes then stop their migration and do not reach their normal resting position in the epithelial surface of the dermis (24).

Three histological types can be distinguished : in Mongolian spot and dermal melanosis melanocytes are sparsely scattered in the dermis, while in blue nevi they are present in greater numbers, forming a tumor and disrupting the normal architecture of the skin (5). The association of melanosis bulbi with dermal melanosis over the distribution of the trigeminal nerve is known eponymously as the nevus of Ota (13).

4.3 Association of Ota with Uveal Melanoma

It is generally accepted that ocular melanocytosis promotes an increased risk for developing a uveal melanoma in the area of pigmentation. According to Singh et al caucasian patients with an Ota nevus have a higher risk to develop a choroidal melanoma in lifetime than patients without oculodermal melanocytosis (1 of about 400 Ota patients followed for live is estimated to develop a uveal melanoma, compared to 1/130.000 in the normal population)(25).

4.4 Reported Association of Ota with Orbital Melanoma

Based on data from the Florida Cancer Data System registry from 1981 through 1993, Margo et al calculated the average annual incidence of primary orbital melanoma : 1.6 % per 10 million people. Tellado (2) studied 21 cases of primary orbital melanoma between 1950 and 1991, and found that 47,5 % were associated with some form of congenital melanosis : 19 had a blue nevus in association with the primary tumor, of which 10 had melanocytosis (5 Ota, 4 ocular and 1 orbital melanocytosis (case of Hagler)).

Lee et al (26) reviewed the literature of primary orbital melanoma in 2002 and found an association with Ota in 15 out of the 35 cases and with blue cell nevus in 4 cases. Six more cases of primary orbital melanoma were published, 5 were associated with nevus of Ota (5-7, 27-29).

Many orbital melanocytic lesions probably form a continuous spectrum. Geram P et al (30) presented a 52 year old man with nevus of Ota, with a large retro-orbital mass infiltrating soft tissue and bone. The exenteration specimen illustrated various stages of melanocytic progression including areas resembling a nevus of Ota, blue nevus, cellular blue nevus, and melanoma. There was also heterogeneity in the overtly malignant sections with some areas displaying expansile nodules of blander appearing spindled cells, whereas other areas were composed of epithelioid cells with higher mitotic counts and zones of necrosis (30).

4.5 Orbital Melanosis

We found 10 report mentioning pigmentation in the orbit. Haim (5) shows a peroperative image of pigmentation of the periosteum and orbital fat, and Rice (9) of pigmentation on the periorbita.

We describe an Ota patient with a uveal melanoma, in which during enucleation pigmentation on the superior, lateral and medial rectus muscles and tendons was seen (Fig 7). Also the ciliary nerves were colored black-grey. Our case is the first reported non-malignant pigmentation on an extraocular muscle is a patient with Ota and illustrated with a photograph.

4.6 Screening for Uveal Melanoma

Among ocular oncologist it is known that patients with oculo(dermal)melanocytosis should be screened for uveal melanoma. In a recent study on uveal melanoma Shields concluded, that all patients with oculo(dermal)melanocytosis should undergo ophthalmic examination and imaging on a twice-yearly basis because this could help with the early detection (11).

Uveal melanomas associated with melanosis have a higher risk of metastasis. Shields at al calculated that patients with uveal melanoma and melanocytosis had a relative risk for metastasis that is 1.6 times greater compared with uveal melanoma without melanocytosis (7). Dutton found 32 reports of melanomas (16 uvea, 6 orbit, 6 intracranial, 4 eyelid) associated with oculodermal melanocytosis. He calculated the incidence of malignant degeneration adjusting for race and found it to be 25% for Whites, 1% for Blacks, 0.5% for Orientals. Orbital melanoma associated with melanosis may possibly also have a higher risk of metastasis.

4.7 Screening for Orbital Melanoma

There is no previous report that highlights the causal relationship between orbital melanosis and orbital melanoma, nor has any advice been given to perform a regular screening for orbital melanoma.

Since oculo(dermal) melanocytosis is a known risk factor for uveal melanoma, melanosis along the whole tract of the trigeminal nerve forms a risk for orbital melanoma.

Buntinx, who published an orbital epithelioid melanoma arising in cellular blue nevus with some mitosis 5 years after initial biopsy, was the first who pointed out that patients with a nevus of Ota or an orbital cellular blue nevus, especially in Caucasian, should be monitored for ocular/orbital involvement and followed closely for signs of rapid growth. There may be a progressive evolution to melanoma from a blue nevus (12, 31). Since melanocytosis is also present in the orbit, all patients with nevus of Ota should not only be screened for uveal melanoma, but also for orbital melanoma.

Whether the intensity of skin or ocular melanosis might correspond with the severity of the orbital melanosis, is not known. The opposite might be possible: if less pigment reached the dermis, more pigment might be trapped in the deeper orbit.

Probably orbital melanocytoma and orbital blue nevi without dermal pigmentation share the same etiology, only the pigment did not reach the skin. In order to confirm these hypothesis, it is important that authors describe the presence (32) or absence (33) of melanocytosis of skin, ocular and orbital tissues during surgery.

From which age should we start screening ? Histology of some of the orbital melanoma associated with orbital melanosis demonstrated few to moderate number of mitosis (table), from which we might hypothesize that these orbital melanomas are not progressing very fast. Which is in line with the clinical reported slowly progressing proptosis in most of the cases.

In the series of primary orbital melanomas of Tellado (2) they found an increased risk of metastasis and intracranial extension if associated with melanocytosis and in melanomas with a mixed cell type. Their mean age at diagnosis was 42 years (ranging from 15 to 84 years) (5), which is 14 years younger than in uveal melanoma not associated with melanocytosis (26).

Our review of orbital melanoma with reported orbital pigmentation contained several very young patients of 15, 17, 18, 27 and 29 years (Table 2). Only 2 of the 11 patients were older than 60 years. Also the review of Lee who listing all reported orbital melanoma before 2002, contained additional young patients of 18, 27, 29 and 32 years old.

Early detection is crucial for survival. Generalists should be aware of the fact that patients with oculodermal melanocytosis have an increased risk to develop an orbital melanoma. The slightest suspicion of proptosis should alert every medical doctor. We advise ophthalmological fundus examination and measurement of orbital proptosis every 2 years from childhood. From the age of 15 years we propose to add an orbital ultrasound by an experienced examiner, although tumors at the apex can be missed. From the age of 40 years we advise an orbital MRI every 2 years.

Table 1. *Site of pigmentation in 230 patients with uveal melanoma associated with oculo(dermal)melanocytosis reported by Shiels et al. and in 127 patients with ocular or oculodermal melanocytosis reported by Teekhasaenee et al. (/: not mentioned)*

Site of Pigmentation	Shields (230 patients)	Teekhasaenee (127patients)
Eyelid	8%	90%
Sclera/episclera	92%	100%
Iris	17%	95%
Choroid	12%	79%
Angle	/	83%
Cornea	/	23%
Lens	/	8%
Optic disc	/	18%
Conjunctiva	/	9%
Orbit	0%	/

Table 2. *Reported orbital melanocytosis in patients with orbital or uveal malignant melanoma (MM), age, gender (m: male, f: female), with localization, picture and pathology of the orbital pigmentations. (+ present, - absent, ? if nothing was mentioned, NA: not applicable)*

Author published	Ota age	Uveal MM	Orbital MM	Capsule	Macrosc Orbital pigmentations	Picture	Histology Orbital Pigmentations
Rottino 1942	? 27m	-	Spindle cells, in bundles or reticular	-	Muscles, Intraconal fat, loose tissue, nerve thrunks, optic foramen	-	Dens mass with free and intracellular melanin (with picture)
Hagler 1965	+ 57m	-	Spindle-shaped, dendritic cells, mitotic figures, also clusters in muscles	no	Periosteum, bony floor, Fat, dural sheath	-	Spindle+dendritic pigmented cells, no mitotic figures, strand-like masses; CBN
Haim 1982	+ 63f	-	large polygonal anaplastic cells, moderate mitosis	fragile	orbital bone, periosteum, orbital fat	+	
Dutton 1984	+ 15m	-	Spindle cells, pleomorphic nuclei, mitosis	pseudo	Clumps throughout orbit	- eyelid	Spindle cells, no nucleoli, no mitosis, brown cytoplasmic pigm

Wilkes 1984	+ Not skin 18m	-	Neoplastic epitheloid cells, some granules of black pigment	+	Connective tissue melanocytes + nodules	-	Spindle- dendriform cells, as cellular blue nevus
Rice 1990	- 17f	-	pleomorphic spindle cells, few mitosis	no	periorbita	+	bleu nevus with heavily pigmented dendritic melanocytes
Koca 1992	+ 38m	-	spindle cell	?	dura, optic nerve, orbital fat and bone	-	polymorph spindle shaped melanocytes, atypia
Koranyi 2000	+ 29m	-	spindle cells in whorls, very few mitosis	fragile	orbital tissue, LRM, posterior bone	-	?
Alilou 2002	+ 48f	+	-	NA	Orbital fat	-	?
Ranjit 2016	+ 87f	-	Large atypical melanocytes	?	Adjacent orbital soft tissue	-	Bland spindle melanocytes
Dickens 2021	- 27 m	-	compacted sheet-like to fascicular growth of spindled to epithelioid melanocytes showing enlarged pleomorphic nuclei, inconspicuous nucleoli. Mitotic figures.	?	sub-epithelial soft tissue of the bulbar conjunctiva and episcleral soft tissue	+	pre-existing blue naevus-like diffuse melanocytosis.
De Groot 2020	+ 54m	Spindle shaped cells in whorls	-	NA	Orbital fat, muscles, muscle tendon	+	Melanocytes with slight atypia, melanin in interstitial tissue and fat

5. Conclusion

Melanocytes of the Ota nevus follow the oculomotor and trigeminal nerves and can therefore be found in any location of the migration path. Because of the increased risk of melanoma at all sites of melanosis, the ophthalmologist should be alert that extraocular melanocytes can remain even after enucleation, and potentially cause orbital melanoma. All medical doctors should know that every patient with the Ota nevus should be screened regularly to excluded choroidal melanoma as well as orbital melanoma. Not only fundoscopy, but also proptosis measurement, ultrasound and orbital imaging should be performed on a regular basis.

6. References

1. Teekhasaenee C, Ritch R, Rutnin U, Leelawongs N. Ocular findings in oculodermal melanocytosis. Arch Ophthalmol. 1990;108(8):1114-20.
2. Tellado M, Specht CS, McLean IW, Grossniklaus HE, Zimmerman LE. Primary orbital melanomas. Ophthalmology. 1996;103(6):929-32.
3. Rottino AK, AS. Primary orbital melanoma. Case report with review of the literature. Arch Ophthalmol. 1942;27:934-49.
4. Hagler WS, Brown CC. Malignant melanoma of the orbit arising in a nevus of Ota. Trans - Am Acad Ophthalmol Otolaryngol. 1965(1):70.
5. Haim T, Meyer E, Kerner H, Zonis S. Oculodermal melanocytosis (nevus of Ota) and orbital malignant melanoma. Ann Ophthalmol. 1982;14(12):1132-6.
6. Koca MR, Rummelt V, Fahlbusch R, Naumann GO. [Orbital, osseous, meningeal and cerebral findings in oculodermal melanocytosis (nevus of Ota). Clinico-histopathologic correlation in 2 patients]. Klin Monbl Augenheilkd. 1992;200(6):665-70.
7. Koranyi K, Slowik F, Hajda M, Banfalvi T. Primary orbital melanoma associated with oculodermal melanocytosis. Orbit. 2000;19(1):21-30.
8. Wilkes TD, Uthman EO, Thornton CN, Cole RE. Malignant melanoma of the orbit in a black patient with ocular melanocytosis. Arch Ophthalmol. 1984;102(6):904-6.
9. Rice CD, Brown HH. Primary orbital melanoma

associated with orbital melanocytosis. Arch Ophthalmol. 1990;108(8):1130-4.

10. 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(5):497-507.
11. Ranjit RU, Leyngold IM, Margo CE. Melanoma-Associated Spongiform Scleropathy in Oculodermal Melanocytosis with Primary Orbital Melanoma. Ocul Oncol Pathol. 2016;2(4):276-9.
12. Dickens TA FM, Gajdatsy A. Mesbah Ardakani N. Primary orbital melanoma arising in an atypical diffuse (plaque-like) blue nevus/melanocytosis: a case report and review of literature. BMC Ophthalmol. 2021;9(21):425.
13. Ota M. Nevus fuseo-caeruleus opthalmomaxillaris. Tokyo Med J. 1939;63:1243-5.
14. Cowan TH, Balistocky M. The nevus of Ota or oculodermal melanocytosis. The ocular changes. Arch Ophthalmol. 1961;65:483-92.
15. Shields CL, Kaliki S, Livesey M, Walker B, Garoon R, Bucci M, et al. Association of ocular and oculodermal melanocytosis with the rate of uveal melanoma metastasis: analysis of 7872 consecutive eyes. JAMA Ophthalmol. 2013;131(8):993-1003.
16. Hidano A, Kajima H, Ikeda S, Mizutani H, Miyasato H, Niimura M. Natural history of nevus of Ota. Arch Dermatol. 1967;95(2):187-95.
17. Gonder JR, Shields JA, Shakin JL, Albert DM. Bilateral ocular melanocytosis with malignant melanoma of the choroid. Br J Ophthalmol. 1981;65(12):843-5.
18. Gonder JR, Ezell PC, Shields JA, Augsburger JJ. Ocular melanocytosis. A study to determine the prevalence rate of ocular melanocytosis. Ophthalmology. 1982;89(8):950-2.
19. Alilou S EM, Kari B, Zaghloul K. Inflammation orbitaire et dégénérescense d'un nevus d'Ota. J Fr Ophthalmologie 2002;25(5):Poster 93.
20. Ito M. Studies on melanin. VII. Mongolian spot cell and blue nevus cell. Tohoku J Exp Med. 1950;52(1-2):119-24.
21. Naumann G, Holbeek, L, Kruse, FE. Applied pathology for ophthalmic microsurgeons. Springer 2008:164.
22. Sharma K, Korade Z, Frank E. Late-migrating neuroepithelial cells from the spinal cord differentiate into sensory ganglion cells and melanocytes. Neuron. 1995;14(1):143-52.
23. Baker CV, Bronner-Fraser M, Le Douarin NM, Teillet MA. Early- and late-migrating cranial neural crest cell populations have equivalent developmental potential in vivo. Development. 1997;124(16):3077-87.
24. Albert D, Miller J, Azar D. Principles and practice of ophthalmology: Saunders; 2008. 3734 p.
25. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC. Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis. Ophthalmology. 1998;105(1):195-8.
26. Lee V, Sandy C, Rose GE, Moseley IM, Cree I, Hungerford JL. Primary orbital melanoma masquerading as vascular anomalies. Eye (Lond). 2002;16(1):16-20.
27. Foster J. An encapsulated orbital melanoma. Br J Ophthalmol. 1944;28(6):293-6.
28. John H, Britto JA. Nonchoroidal intraorbital malignant melanoma arising from naevus of Ota. J Plast Reconstr Aesthet Surg. 2010;63(4):e387-9.
29. Radhadevi CV, Charles KS, Lathika VK. Orbital malignant melanoma associated with nevus of Ota. Indian J Ophthalmol. 2013;61(6):306-9.
30. Gerami P, Pouryazdanparast P, Vemula S, Bastian BC. Molecular analysis of a case of nevus of ota showing progressive evolution to melanoma with intermediate stages resembling cellular blue nevus. The American Journal of dermatopathology. 2010;32(3):301-5.
31. Buntinx-Krieg T, Ouyang J, Cartwright M. An Orbital Malignant Melanoma Arising in Cellular Blue Nevus in a Patient with Nevus of Ota. Cureus. 2016;8(7):e698.
32. Tregnago AC, Furlan MV, Bezerra SM, Porto GC, Mendes GG, Henklain JV, et al. Orbital melanocytoma completely resected with conservative surgery in association with ipsilateral nevus of Ota: report of a case and review of the literature. Head & neck. 2015;37(4):E49-55.
33. Nasr HE, Nouh MA, Ahmed RA, Elhusseiny AM. Orbital melanocytoma: When a tumor becomes a relieving surprise. Am J Ophthalmol Case Rep. 2018;10:124-7.