

Review Article

Pigmented Epibulbar Lesions: Overview

Furdova Alena*, Alsalman Ali Jameel, Krcova Ivana, Horkovicova Kristina and Furdova Adriana

Department of Ophthalmology, Medical School, Comenius University, Bratislava, Slovakia

Abstract

Eyes can be affected by a wide variety of epibulbar lesions. The incidence and prevalence of the epibulbar lesions is significantly high, with an incidence of 89.8% of the benign lesions as compared to the malignant lesions that accounted for 10.2% of the lesions.

Considering the significance of the knowledge of the different types of epibulbar lesions, there is a need to perform a brief discussion of these lesions to develop the information of these lesions among the general population and the healthcare professionals. This would enable the successful diagnosis of the different types of epibulbar lesions.

Epibulbar pigmented lesions include conjunctival epithelial melanosis, conjunctival freckle, primary acquired melanosis, conjunctival nevus, congenital ocular melanocytosis, and malignant melanoma.

Keywords: Conjuntival pigmented tumor; Nevus; Melanoma; Primary acquired melanosis; Racial melanosis

Introduction

The complexity of the structure of eyes is extreme as they have a vital function that requires several small structures to perform the functioning of vision. Eyes can be affected by a wide variety of epibulbar lesions. The incidence and prevalence of the epibulbar lesions is significantly high [1].

The incidence of benign lesions is extremely increasing with an incidence of 89.8% of the benign lesions as compared to the malignant lesions that accounted for 10.2% of the lesions (Toshida, 2012). Another study has also observed similar results as the prevalence of malignant lesions was 24.1% while that of the benign lesions was 75.9%. Most common of these lesions were basal cell carcinoma, melanoma, squamous cell carcinoma and sebaceous cell carcinoma. This signifies the importance of the in-depth knowledge of the anatomy of the human eye and the different types of lesions that can affect the eye.

There is a variation in the prevalence of the lesions with regards to the region. Considering the significance of the knowledge of the different types of epibulbar lesions, there is a need to perform a brief discussion of these lesions to develop the information of these lesions among the general population and the healthcare professionals. This would enable the successful diagnosis of the different types of epibulbar lesions.

Conjunctiva: Anatomical Notes

Conjunctiva is thin mucous membrane that lines inner eyelid (tarsal or palpebral portion) and anterior surface of ocular globe (bulbar portion). Conjunctiva has protective function and also allows eyelids to move smoothly over the globe, it is full with lymphatic channels connecting to parotid and submandibular nodes. The palpebral conjunctiva starts at the mucocutaneous junction of the lid margins and is firmly attached to the posterior tarsal plates. The underlying tarsal blood vessels can be seen passing vertically from the lid margin and fornix.

The forniceal conjunctiva is loose and redundant and may be thrown into folds. It contains accessory lacrimal tissue, ductules of main lacrimal gland and lymphoid follicles. The bulbar conjunctiva covers the anterior sclera and is continuous with the corneal epithelium at the limbus. Radial ridges at the limbus form the palisades of Vogt. The stroma is loosely attached to the underlying Tenon capsule, except at the limbus, where the two layers fuse. A plica semilunaris (semilunar fold) is present nasally, medial to which lies a fleshy nodule (caruncle) consisting of modified cutaneous tissue containing hair follicles, accessory lacrimal glands, sweat glands and sebaceous glands.

Microscopically conjunctiva consists of three layers- epithelium, adenoid layer and fibrous layer [2]. Epithelial layer is the most superficial layer of the conjunctiva and is made up of epithelial cells arranged neatly in layers just like in other mucous membranes of the body. This layer is about 5-cell thick in the regions of the limbus and the eyelid margin, about 3-cell thick in the fornices and over the sclera (bulbar part) and 2-cell thick behind the eyelids (tarsal part). The adenoid layer contains a fine meshwork of fibrous tissue with lymphocytes, cells of the immune system. This layer is absent at birth and develops only after the baby is three or four months old. The fibrous layer is deeper and consists of connective tissue fibres and blood vessels and nerves of the conjunctiva.

Blood and Nerve Supply of the Conjunctiva

Arterial supply of conjunctiva derives from peripheral Tarsal arcades, marginal Tarsal arcades and the anterior ciliary arteries.

The nerve supply to the conjunctiva is derived from the first division of the trigeminal nerve. The nerves to the lid innervate most of the conjunctiva. These nerves comprise the infratrochlear branch of the nasociliary nerve, the lacrimal nerve, the supratrochlear and supraorbital branches of the frontal nerve, and the infraorbital nerve from the maxillary division of the trigeminal nerve. The limbal area is innervated by branches from the ciliary nerves. All nerves form a network in the conjunctiva and terminate either peripherally in various forms of specialized endings or on blood vessels and epithelial cells. The majority of nerve endings in the conjunctiva are free, unmyelinated nerve endings. They form a sub-epithelial plexus in the superficial part

*Corresponding author: Furdova Alena, Department of Ophthalmology, Medical School, Comenius University, Bratislava, Slovakia, Tel: +421903301047; E-mail: alikafurdova@gmail.com

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of the substantia propria. Many of these fibers end on blood vessels, and others form an intraepithelial plexus around the base of epithelial cells and send free nerve endings between cells [2].

Classification of the Epibulbar Lesions

There are two types of the epibulbar lesions that include the pigmented and the non-pigmented lesions. These lesions are further classified into benign, premalignant and malignant lesions. The probability of the incidence of malignant lesions is only fifteen to twenty percent of all the periocular lesions of the skin; therefore, most of the lesions are benign. The other classification based on clinical classification (TNM) or pathological classification (pTNM) which shows the clinical and pathologic features of the lesions.

Pigmented epibulbar lesions

Lesions that are pigmented are one of the major reasons of surgery in the United States. These lesions are considered undesirable by the patients due to their appearance, color, location and size (Kilmer, 2000). The pigmented lesions can be either benign or malignant. These lesions include conjunctival epithelial melanosis, conjunctival freckle, primary acquired melanosis (PAM), conjunctival nevus, congenital ocular melanocytosis, and melanoma.

TNM Classification of Epibulbar Lesions

This classification can be clinical (eTNM) or pathological classification (pTNM) which shows the clinical and pathologic features of the lesions and how it extended is.

Clinical classification (eTNM)

- (T) Primary tumor:
- TX Primary tumor cannot be assessed.
- T0 No evidence of primary tumor
- T1 Tumor(s) of bulbar conjunctiva occupies 1 quadrant or less
- T2 Tumor(s) of bulbar conjunctiva occupies more than1 quadrant
- T3 Tumor(s) of conjunctiva fronix or palpebral conjunctiva or caruncle
- T4 Tumor invades eyelid, cornea or orbit
- (N) Regional lymph nodes:
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis
- (M) Distant metastasis
- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis
- Pathologic classification (pTNM):
- (pT) Primary tumor:
- pTX Primary tumor cannot be assessed
- pT0 No evidence of primary tumor
- pT1 Tumor(s) of bulbar conjunctiva occupies 1 quadrant or less and 2mm or less in thickness

- pT2 Tumor(s) of bulbar conjunctiva occupies more than 1 quadrant or less and 2mm or less in thickness
- pT3 Tumor(s) of the conjunctival forinx or palpebral or caruncle or bulbar conjunctiva, more than 2 mm in thickness
- pT4 Tumor invades eyelid, cornea or orbit
- (pN) Regional lymph node:
- pNX Regional cannot be assessed
- pN0 No regional lymph node metastasis
- pN1 Regional metastasis
- (pM) Distant metastasis:
- pMX Distant metastasis cannot be assessed
- pM0 No distant metastasis
- pM1 Distant metastasis
- Stage group: No stage grouping is recommended at this time. Histopathologic type: This categorization is applied only to melanoma of conjunctiva
- Histopathologic grade: This grade represent the origin of the primary tumor
- GX Origin cannot be assessed
- G0 PAM
- G1 Malignant melanoma arise from a nevus
- G2 Malignant melanoma arise from a PAM
- G3 Malignant melanoma arise de novo

Pigmented Epibulbar Lesions

Conjunctival epithelial melanosis (Racial)

Conjunctival epithelial melanosis occurs due to the production of melanin in an increased amount. Melanin is a pigment that is produced primarily upon exposure to the UV rays. It mostly occurs in the individuals who are dark skinned. It can affect both eyes but there might be some difference in the intensity as it can be asymmetrical. It is usually presented during the early years of life but the prominence of melanosis occurs in the early adulthood [3].

Epidemiology: Approximately 1-2% of the ocular melanomas are accounted by the conjunctival epithelial melanosis. The incidence of conjunctival epithelial melanosis has increased during 1973 to 1999 that accounted for 5.5% biannually. It has no restriction of the gender but the incidence is commonly observed in the middle age or in the adulthood. The incidence of conjunctival epithelial melanosis is lower in the individuals belonging to Africa or in the individuals of African-American origin. The highest incidence is observed in the Caucasian population [4].

Pathogenesis: It is difficult to understand the molecular pathogenesis of the conjunctival epithelial melanosis. There have been some observations in the past that suggest the association of the mutations in BRAF gene to be responsible for the development of conjunctival epithelial melanosis. It can be developed by a melanocytic lesion that is already present. The most common occurrence is from the primary acquired melanosis that accounts for 75%. Furthermore, it can also be developed from a conjunctival nevus related to 20% of the conjunctival epithelial melanosis. The most important risk factor

for the development of conjunctival epithelial melanosis is solar radiation's exposure.

Clinical features: The appearance of the conjunctival epithelial melanosis lesion is fleshy that comprise of elevated lesions. The pigmentation of these lesions is variable and the primary location of these lesions is temporal bulbar conjunctiva or the nasal area. Those lesions that arise from primary acquired melanosis can be diffuse or circumscribed. Extension of lesion can occur towards the margin of the eyelid or could be adjacent to the margin of the eyelid. It could also be located towards the orbit or the globe [4].

Predictive signs of conjunctival epithelial melanosis: The most common signs of conjunctival epithelial melanosis include the presence of patchy pigmentation that is brownish in color and areas are commonly flat which are scattered around the conjunctiva. However, the intensity of these characteristics is more prevalent at the limbus. The region of the anterior ciliary vessels having perforating branches has more intensity of these lesions. The intensity of these lesions is sometimes also increased at the intrascleral nerve entering the sclera. The location of the pigmentation of the conjunctival epithelial melanosis is seen to be near the epithelium when observed from the slit lamp. This results in the free movement of the pigmentation over the exterior portion of the globe [3].

Diagnosis: Diagnosis of conjunctival epithelial melanosis requires the examination of tarsal and bulbar conjunctivae. It is also significant to perform the examination of rim of the orbit as the rate of recurrence is high. Regional lymphoadenopathy must be examined in all the patients who have been diagnosed or are under treatment or in followup period. CT scan of the entire body can be performed along with the lymphoscintigraphy, ultrasonography, and ultrasound [4].

Management: Immediate referral should be made to the ophthalmological services upon suspicion of conjunctival epithelial melanosis. Surgical excision can be performed for the management of conjunctival epithelial melanosis. Histopathologic evaluation of the dissected lesions is required to confirm the diagnosis of conjunctival epithelial melanosis. Detection in the early stages and excision of the dysplastic lesions provides the best prognosis (Figures 1 and 2).

Conjunctival freckle

An ephelis (freckle) is similar to those of the skin and caused due to the increased production of the pigment melanin in the basal conjunctival epithelium. It most often involves the bulbar conjunctiva near the limbus, but it may involve the bulbar or palpebral conjunctiva [5]. They are not easily identified by the patient and mostly patient remains unaware of their presence. They are revealed upon an ophthalmological examination of eye by putting drops that dilates the pupil. They do not cause damage to vision but they can be dangerous as they can convert into malignant lesions called melanomas. Conjunctival freckle do not require treatment as they are not harmful to the patient. They are made up of cells that contain brown pigments.

Epidemiology: The incidence of conjunctival freckle is accounts for approximately less than 10% in the population. The prevalence of conjunctival freckle is dependent on the race of the individual. Increased prevalence is observed among the whites that relates to 4.1% of the incidence among the white population. The second highest prevalence rate is among the Chinese population that accounts for 2.9% followed by Hispanics. The lowest prevalence is among the afro american people.

Pathogenesis: Conjunctival freckle is a pigmented lesion, it is





Figure 2: Racial melanosis (foto Alena Furdova, Dpt. Ophthalmology, Comenius University, Bratislava).

brown, patchy, flat lesion with irregular borders. It most often involves the bulbar conjunctiva near the limbus, but it may involve the bulbar or palpebral conjunctiva .They are mostly gray but can also be present as brown or yellow freckle that can also be of variable pigmentation. It can also have spots on the surface that are termed as drusen. It also indicates the retention of these products over an increased period of time that has resulted in the accumulation to generate spots on the surface. The conversion of drusen into a conjunctival freckle has not been studied; therefore, the duration of the conversion cannot be identified.

Diagnosis: Diagnosis of the conjunctival freckle requires careful eye examination by an ophthalmologist. Proper documentation of the eye examination is also required in this regard. Sometimes testing is required for diagnosing conjunctival freckle which could include ultra sound testing, angiogram of the interior portion of the eye, and specialized photography. These tests are beneficial for the documentation of the characteristics, size and shape of the conjunctival freckle. This enables to determine whether there have been some changes or not. The histology consists of increased pigmentation

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in the basal cell layer of the conjunctival epithelium the number of melanocytes is normal or decreased [5].

Management: Treatment is not required for a conjunctival freckle and there is unavailability of the procedures that could be performed to safely remove these freckles. However, regular eye examination should be performed to reduce the incidence of development of a conjunctival freckle from benign to malignant form. Individuals with conjunctival freckle should try to sustain from UV rays as the production of pigmentation is commonly associated with exposure to UV rays. Sunglasses can be worn to prevent exposure of the eyes to direct sunlight to prevent the transition of benign form into malignant.

Primary Acquired Melanosis (PAM):

Primary Acquired Melanosis (PAM) is categorized mostly as malignant and premalignant lesion of the epibulbar. The most common occurrence of primary acquired melanosis is in the white individuals who have a fair complexion. It is a unilateral condition which has two types. One type is primary acquired melanosis with atypia and other type is primary acquired melanosis without atypia. Primary acquired melanosis with atypia is premalignant lesion while primary acquired melanosis without atypia is a benign lesion (Figure 3).

Epidemiology: It usually occurs in the individuals who are middleaged. The most common incidence of primary acquired melanosis among the Caucasian. Its prevalence is increased in the regions having high temperature with sunlight. Therefore, prevalence is increased upon exposure to sunlight [4].

Predictive signs of Primary Acquired Melanosis (PAM): The appearance of these lesions is unilateral along with the presentation of multifocal or unifocal segments of flat pigmentation that are located in the superficial layers of specific regions of conjunctiva. It can also involve the peripheral cornea. These pigments can also occupy the bulbar and palpebral conjunctiva due to which it is required to invert the upper eyelid for performing the inspection of tarsal conjunctiva. There is no significant difference in the clinical features of the primary acquired melanosis without and with atypia. Therefore, there is a need to perform histopathological examination [4].

Pathophysiology: Primary acquired melanosis with atypia has an increased number of intraepithelial melanocytes which results in the presentation of pleomorphism. In case of severity it can be referred to as melanoma which has 50% probability of exhibiting infiltration malignancy during 5 years. Primary acquired melanosis without atypia is benign lesion which has an intraepithelial proliferation of melanocytes of the epithelium. It does not pose the risk of transformation into



Figure 3: Primary acquired melanosis (male patient, 48 years old - foto Alena Furdova, Department Ophthalmology, Comenius University, Bratislava).

malignant form. It usually presents after 45 years of age [3].

Diagnosis: Immunohistochemistry should be performed that by taken biopsy sample since it is difficult to differentiate between the primary acquired melanosis with atypia and without atypia. Presence of small segments of lesions of primary acquired melanosis is common among the population. Presence of lesion with diameter of more than 5mm must be referred to an ophthalmologist. If the lesion progresses than it must be documented and diagnosed by performing diagnostic testing. Involvement of the cornea must also be reported as it is also included in the diagnostic characteristics of primary acquired melanosis. Fornial conjunctiva or tarsal conjunctiva can also be involved which is also a diagnostic feature of the primary acquired melanosis. Dilated supplying vessel can also be present that indicates the possibility of presence of primary acquired melanosis. A distinct nodule can also arise from a flat lesion which must be examined to diagnose the presence of primary acquired melanosis [4].

Management: Lesions that are presenting atypia must be treated with topical mitomycin C or cryotherapy. Treatment can also include the excision of the lesions that are small. Incision biopsy can be performed for the lesions that are large. This biopsy includes the incision from various sites of the lesion [3]. Small patches of PAM are common in the population. Certain signs that require urgent referral to ophthalmology however, include:

- 1. Lesion diameter $\geq 5 \text{ mm}$
- 2. Presence of distinct nodule arising in an otherwise flat lesion
- 3. Documented progression of the lesion
- 4. Corneal involvement
- 5. Involvement of the forniceal or tarsal conjunctiva
- 6. Presence of dilated supplying vessels

Conjunctival nevus

Conjunctival nevus is the most common type of the melanocytic conjunctival lesions. It has very low risk of transformation into malignant form of the lesion. This accounts for only 1% of the transformation rate. It has similarity to cutaneous nevus, the only difference is in the absence of dermis as the dermal is replaced by the stromal and subepithelial in nomenclature. There are three types of the conjunctival nevi that include junctional nevi, compound nevi and subepithelial lesions (Figure 4).

Epidemiology: The conjunctival nevus is one of the most common benign tumors of the ocular surface [6]. These are the discrete melanocytic lesions that are most commonly observed. The initial appearance of the conjunctival nevus is in the first ten years of life in which it appears as a flat pigmented lesion. Its incidence is not dependent on the gender; however, the prevalence is usually among the Caucasian population. Its association in this population is with familial atypical mole and melanoma syndrome. This syndrome is an autosomal condition which is characterized by increased incidence of ocular and cutaneous melanoma. The incidence of this lesion is in the individuals with presence of melanoma in the family. It usually appears during the 1st to 2nd decades of life with the presentation of the lesion in the form of unilateral and solitary lesion. The lesion is also pigmented and which is slightly elevated and discrete. The intraepithelial bulbar lesion has variable size and the incidence is usually in the juxtalimbal area. There is variation in the extent of pigmentation with the exception of possibility of some virtually non-pigmented lesions. There is frequent presence of cystic spaces that are present within the nevus. There is



possibility of appearance of congested and pink lesions among children and adolescents. The incidence of lesion at an unusual site like fornical or palpebral conjunctiva indicates the possibility of potential malignant lesion. Presence of prominent supplying vessels is also indicative of development of potential malignant lesion. Sudden increase in the pigmentation or growth of the lesion also predicts the presence of a malignant lesion. If the lesion develops after second decade than it also demonstrates a malignant lesion [3].

Pathophysiology

Presence of conjunctival nevi is not always pigmented as 16% of the cases of conjunctival nevi are found to be clinically amelanotic. It usually occurs at the bulbar conjunctiva with incidence of 67-72% with specific incidence at the interpalpebral region. The appearance also occurs at the caruncle while the least possibility of incidence is at the tarsus. Therefore, the presence of the lesions at tarsus must be considered specifically as high suspicious for malignancy until proven. These lesions are discrete and mobile and with the passage of time the pigmentation of these lesions can also become increased that represents concerning features. There is a possibility of increased pigmentation and size in the children particularly after puberty which does not indicates a malignant transformation. Appearance of clear cysts that are more evident in the presence of non-pigmented lesion represents a pathognomonic feature [4].

Diagnosis: The diagnosis of conjunctival nevus can be performed by biomicroscopy with slit lamp. In order to detect the region of the presence of the intra-lesional cysts, OCT of the anterior segment can be preformed. It is also possible to use the immunohistochemical markers to detect the lesions that are not clinically diagnosed. However, the antigen specific to melanoma can demonstrate a positive reaction to both melanoma and nevus.

Management: Indication of treatment is limited only for the cosmetic reasons. It is not required to perform the treatment of the lesions that are small as their resolution is often spontaneous. Treatment of large lesions can be performed through cryotherapy and excision. In cases where there is recurrence of the lesion, treatment includes laser vaporization with carbon-dioxide, application of topical mitomycin C, subconjunctival alpha-interferon and oral cimetidine [3].

Congenital ocular melanocytosis

Congenital ocular melanocytosis is a melanocytic hyperplasia that is unilateral and characterized by hyperpigmentation of the orbital

tissues, sclera, meninges and episclera. It has two clinical divisions that include oculodermal melanocytosis and ocular melanocytosis. Oculodermal melanocytosis is referred to the condition when there is involvement of the periocular skin. Both of these clinical conditions are non-hereditary.

Epidemiology: The incidence of congenital ocular melanocytosis is most commonly observed in the Caucasians. This accounts for nearly 0.04% of the cases of congenital ocular melanocytosis. The condition is not prevalent among other populations of the world like Africans and Asians [4]. There are no differences in frequency based on laterality or gender [7].

Predictive signs of congenital ocular melanocytosis: The appearance of the ocular surface lesions is in the form of multifocal segments of episcleral and sclera slate-grey pigmentation which is immobile. The distribution of the pigmentation can be either sectorial or diffused. It occasionally involves the peripheral cornea also. There is also presence of the iris mammillations that are numerous, villiform, tiny, brown nodules that occupies the iris stroma. Pigmentation in the background fundus is higher than that in the opposite eye. There is also possibility of the presence of the fundus hyperpigmentation with sectoral distribution.

Diagnosis: Diagnosis of the congenital ocular melanocytosis is based on presentation with classic findings noted during slit-lamp and external ocular examination. Histopathologically, of the ocular melanocytosis is characterized by the presence of dendritic melanocytes in the areas of hyperpigmentation [7]. Primary acquired melanosis of the conjunctiva might be confused with ocular melanocytosis, but such conjunctival pigmentation is movable over the sclera and unassociated with iris heterochromia and uveal hyperpigmentation. Careful regular follow-up is recommended for early detection of uveal melanoma in ocular melanocytosis [8].

Management: In and of itself, congenital ocular melanocytosis is a benign condition that does not require treatment [7]. Review of the patients should be performed by the ophthalmologist. This is recommended due to the risk of meningeal, uveal and orbital malignant melanomas. It is also advice do perform periodic intraocular pressure measurements [4]. Prognosis Visual impairments that arise in the context of ocular melanocytosis are due to the development of complications including uveitis, glaucoma, and cataract. Additionally, the association with an increased frequency of uveal melanoma in the affected eye has further implications on morbidity and mortality [7].

Malignant melanoma

The prevalence of melanoma can be predicted by the fact that it accounts for 2% of the ocular malignancies that are caused in the individuals. Melanomas are rare; they can arise without a preexisting conjunctival nevus or due to malignant transformation in case of Primary Acquired Melanosis (PAM) [9]. Conjunctival melanoma originates de novo in about 5 percent of all cases, from preexisting conjunctival PAM in 75 percent, and from nevi in 20 percent. It is an aggressive tumor and recurrence rates may be as high as 51 percent over 10 years, especially if the tumor is not located at the limbus and has not been completely excised at the time of surgery [10].

Predictive signs of melanoma: The presentation is most commonly observed in the sixth decade with the exception of patients suffering from dysplastic nevus syndrome that occurs rarely can develop multiple melanomas later in life. The appearance of the melanoma that arises from a nevus that is pre-existing is grey or black vascularized

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nodule which can be attached to the episclera. The common region of the appearance of lesion is limbus but it can also develop any other location in the conjunctiva. Appearance of the amelanotic lesions is smooth fish-flesh and pink which can cause diagnostic problems (Figure 5).

Diagnosis: The diagnosis of melanoma includes the identification of presence of large nevus, melanocytoma, extraocular extension, pigmented conjunctival carcinoma and ciliary body melanoma in the individuals with dark skin. A classic conjunctival melanoma presents as a pigmented nodular lesion usually located at the limbus over or adjacent to an area of PAM in Caucasian patients during the sixth or seventh decade of life. Conjunctival melanoma may uncommonly be amelanotic or reddish-pink in color, simulating a malignant epithelial neoplasm, such as conjunctival intraepithelial neoplasia or squamous cell carcinoma or a more benign inflammatory process, such as nodular episcleritis or pyogenic granuloma. The precursor PAM can also present as PAM sine pigmento. The presence of cysts in an amelanotic lesion favors a diagnosis of amelanotic nevus. Determining the margins of amelanotic lesions can be troublesome, and careful evaluation at the slit lamp should be done before surgical excision. Excisional biopsy is always preferred. Incisional biopsy may promote tumor seeding and lead to local scarring. The best option is a complete excisional procedure. This will give the patient the highest likelihood for an optimal outcome while minimizing the risks. If the area of suspected tumor or the area of pigmentation is extensive, map biopsies are justified. The best way to make the correct diagnosis is by histopathologic evaluation. But conjunctival melanoma is a great mimic. The surgical plan starts at the slit lamp, with careful evaluation of lesion extension and margins, detailed schematic drawings and photodocumentation [10].

Management: Excision of the circumscribed lesions can be performed through cryotherapy and wide margin. Adjunctive radiotherapy should be administered if histology demonstrates extension of the tumor deeper into the surface of the specimen [3]. Malignant melanoma of the conjunctiva most often arises from PAM, but can also arise from a preexisting nevus or de novo. It usually arises in middle-aged to older adults, but less common cases of conjunctival melanoma in children have been observed. Approximately, 1% of all conjunctival melanomas occur in children. Conjunctival melanoma shows considerable clinical variability, as it can be pigmented or nonpigmented, pink, yellow or brown in color and involve the limbal, bulbar, forniceal or palpebral conjunctiva [11].

Orbital melanomas

Primary melanocytic orbital tumors include melanoma, melanoctic



Figure 5: Conjuntival malignant melanoma in the fornix (foto Alena Furdova, Department Ophthalmology, Comenius University, Bratislava).

hamartoma and Melanotic Neuroectodermal Tumor (MNET) of infancy. Primary orbital melanoma usually originates from congenital ocular melanoctyosis or hypercellular blue nevus that affects the orbital tissue. Rarely; it can arise from the optic nerve or after orbital irradiation for rhabdomyosarcoma. Melanoma from melanocytosis and from blue nevus is similar [12].

Epidemiology: Primary or secondary orbital melanomas are extremely rare tumors; they represent less than 1% of primary orbital neoplasms. Over 90% of primary orbital melanomas arise from melanocytes (congenital ocular melanosis, oculodermal melanosis) [13].

Clinical features: The underlying congenital melanocytic lesion may be evident anteriorly as ocular melanocytosis or blue nevus, but it is often subclinical in the orbit more posteriorly, until it spawns a melanoma later in life. The melanoma that arises from blue nevus or congenital melanocytosis is generally circumscribed, even though the underlying congenital pigmentation is diffuse or patchy. Proptosis in a patient with either congenital ocular melanocytosis or episcleral blue nevus should arouse suspicion for a primary orbital melanoma or orbital extension of uveal melanoma.

Pathology: Grossly and at surgery, orbital melanoma is generally a brown or black circumscribed mass. Microscopically, it is composed of spindle or epitheliod melanoma cells. In many cases, residual areas of cellular blue nevus can be identified. Extensive tumor necrosis is common. Immunohistochemistry demonstrates a positive reaction to melanoma - specific antigens.

Diagnosis: CT and MRI, enhancing mass in orbital soft tissue, usually in the extraconal space, sometimes in an extraocular muscle. MRI may help to detect the melanin content in the lesion. With time, the tumor can breach its pseudocapsule and diffusely invade the orbit. As part of a diagnostic workup for proptosis, the clinician should inspect the eyelid skin and episclera to look for a blue nevus and perform ophthalmoscopy to rule out uveal melanoma. Melanomas arising in the orbit can present diagnostic and management challenges to the physician. Most orbital melanomas arise from the uveal tract, conjunctiva, eyelids or sinuses and infrequently, as metastases from distant primary sites. Approximately 90% of primary orbital melanomas arise from melanocytes found in congenital ocular melanocytosis (including blue nevus and cellular blue nevus), orbital melanocytosis, or oculodermal melanocytosis (nevus of Ota). Orbital biopsy may be required to diagnose orbital melanoma when noclinical evidence of melanocytosis of the periocular tissues or uveal tractis present. Even with an orbital biopsy, the histopathologic diagnosis can often be difficult, especially if the tumor is amelanotic [14].

Management: Melanomas arising in the orbit can present diagnostic and management challenges to the physician. The entire tumor should be remove and intact, because the orbital melanoma usually well circumscribed. An incisional biopsy of circumscribed orbital mass in the setting of congenital ocular melanocytosis is contraindicated if there is a chance of removing the tumor intact. Orbital melanoma is more likely can recur or metastasize to distant organs if not removed intact. The surrounding flat congenital pigmented should be examined at surgery, biopsied and treated with heavy cryotherapy or recurrent orbital melanoma should usually be managed by eyelid sparing orbital exonerations [12]. Exenteration which is surgical removal of the entire orbital contents, including the globe, optic nerve, extraocular muscles, lacrimal gland and lacrimal drainage system, as well as the orbital fibroconnective and adipose tissues, is undertaken only in extreme circumstances, such as malignant invasive tumors or adenoid cystic carcinoma. Over 90% of orbital exenterations are performed as a last resort for invasive neoplasms (Figure 6).

Discussion

Melanocytic lesions of the ocular adnexa include nevi, Primary Acquired Melanosis of the Conjuctiva (PAM) with or without atypia, and Malignant Melanoma (MM). The classification divides them into congenital and acquired lesions, which are generally unilateral. Conjunctival nevus is the most common type of benign tumors of the conjunctiva. This lesion is usually congenital, with the highest incidence in the second and third decade of life if they are pigmented. Conjunctival melanoma has an incidence of less than one per million per year and represents only 2% of all malignant diseases of the eye. It is lethal neoplasm, with an average 10-year mortality rate of 30%. Melanoma of the conjunctiva tends to present in adulthood, especially in Caucasian population. The median age at diagnosis is 60 years. Melanoma arises from three sources - PAM, nevus or de novo. Approximately 75 % of cases have PAM, up to 20 % of patients have history or microscopic evidence of a benign nevus and 5 % are de novo melanomas. Melanomas of the conjunctiva are deeply pigmented, lightly pigmented or amelanotic. Their margins may be discrete or diffuse. They can be unifocal or multifocal. Side effects of this tumor are dilated supplying vessels and degenerative changes of the cornea when the tumor involves cornea. Histopathology of these lesions shows a loss of normal polarity. The cells are atypical, with an increased nuclear to cytoplasmic ratio and scattered mitoses. Clinical examination findings involve discrete well defined congenital lesions that are most commonly found on the interpalpebral bulbar conjunctiva. These lesions can also involve the caruncle, plica, and lid margin. They are rarely found in the fornix. Histopathological findings show benign proliferation of nevus cells present predominantly in the substantia propria. Histologically, PAM is characterized by melanocytes in the vicinity of the basement membrane of the epithelium with or without atypical cells and amplified pigmentation. In PAM without atypia, there is almost never a malignant transformation. Treatment involves either observation or local excision if the lesion is unsightly or shows unusual growth. The treatment is necessary to reduce the possibility of spread of the tumor. Melanoma of the conjunctiva spreads into the regional lymphatics. The median time of regional and systemic metastases is about 2 years, the risk of malignant melanoma of the conjunctiva within 10 years is up to 30 %. All suspicious lesions should be histologically examined to confirm the clinical diagnosis. Risk factors for metastasis include more than 2 mm in thickness, the participation of nonbulbar conjunctiva,



Figure 6: Conjunctival melanoma in stage T4 infiltrating the orbit (foto Alena Furdova, Department Ophthalmology, Comenius University, Bratislava).

caruncular disease, medial tumor location and tumor recurrence. Therefore, local excision with a "no-touch technique" is the goal of treatment. Diffuse disease can be treated by cryotherapy or topical adjuvant chemotherapy with mitomycin C (MMC). If the disease is too extensive for ocular conservation, exenteration is performed. Some authors advocate sentinel lymph node biopsy in high-risk cases. Good results in tumor control can be achieved by brachytherapy. Latest trends in therapy with interferon alfa2b were reported by the PAM. Mitomycin C is originally an antibiotic from Streptomyces caespitosus and belongs to the group of alkylating agents and inhibits DNA synthesis. MMC reacts under aerobic conditions with molecular oxygen and intermediates are produced. These in turn are known for their cytotoxic effects of lipid peroxidation. Mitomycin C is used in ophthalmology for many years to prevent recurrence of pterygium and in conventional glaucoma surgery. Ocular use of topical MMC helps in prevention of pterygium recurrence in the treatment to prevent transformation to squamous neoplasia of the conjunctiva [15-19].

There is limited knowledge of the common eye diseases and conditions among the medical staff which suggests the need of increased knowledge of these conditions. Therefore, further studies are required to describe the various types of the epibulbar lesions to enhance the information of the healthcare staff for improved diagnosis and treatment of the various conditions of eye. The results of this thesis support the fact that there is an increased requirement of the improved knowledge of these conditions so that further treatments can be developed by performing further research. Future studies are required to focus on the development of treatment procedures that can be performed. Surgical procedures should be explored to demonstrate their significance and efficiency for the treatment of the epibulbar pigmented and non-pigmented lesions. It is recommended to perform further studies of the various eye conditions.

The significance of eyes has been demonstrated in the literature and the importance of vision is also undeniable. Eyes are responsible for the formation of images corresponding to vision by collecting the light sent by various objects. There are several conditions that can affect the eyes causing disturbance in the formation of vision. Epibulbar lesions are the lesions that are formed in the eyeballs particularly in the conjunctiva and cornea. These lesions are classified into two distinct types that include pigmented and non-pigmented epibulbar lesions. The pigmented epibulbar lesions are those lesions that have pigments while the non-pigmented lesions are those that are translucent or transparent due to the absence of the pigments.

There is an increased need of the improved knowledge of these conditions so that further treatments can be developed by performing further research. Further studies are recommended to provide an indepth analysis of the effectiveness of different treatments that can be used for the treatment of the epibulbar pigmented lesions.

Conclusion

Epibulbar pigmented lesions include conjunctival epithelial melanosis, conjunctival freckle, primary acquired melanosis, conjunctival nevus, congenital ocular melanocytosis, and malignant melanoma. The benign pigmented epibulbar lesions are not harmful but can transform into malignant form of the lesion. Most of the small benign lesions do not require surgical removal or treatment. Chemotherapy can be performed in some cases along with the administration of immunological antibodies including interferon. Topical agents can also be applied to the lesions for the treatment of various types of lesions.

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