

## **Conjunctival Melanosis: Review of the Literature**

Jerman M Alqahtani, MD\*

**Background:** Conjunctival melanoses are a common clinical finding of flat granular melanotic pigmentation of the conjunctival epithelium. Differential diagnosis of these lesions is difficult and there is much confusion in the literature regarding their classification.

**Objective:** To update the readers' knowledge about conjunctival melanosis and its clinicopathologic classification.

**Method:** The author searched electronic databases for primary studies (MEDLINE, EMBASE, and CINAHL) and systematic reviews (PubMed) from the early 1960 when these lesions were described until the end of December 2012.

**Selection Criteria:** English-language systematic reviews; randomized, controlled trials; and quasi-randomized, controlled trials for conjunctival melanosis.

**Data collection and analysis:** Abstracts were screened and data were extracted and reviewed by the author.

**Result:** The conjunctival melanoses are a group of diseases characterized by flat granular melanin-pigmentation of conjunctival epithelium. Because differential diagnosis of these lesions is difficult, there is much confusion in the literature regarding their classification.

**Conclusion:** Benign, melanosis should be divided based on clinical findings into complexion-associated melanosis, secondary melanosis, ephelis, and primary acquired melanosis without atypia. Primary acquired melanosis with atypia is more likely to evolve into a malignant melanoma.

*Bahrain Med Bull 2013; 35(4):*

Melanosis is an increased melanotic pigmentation. The conjunctiva can be affected by a variety of melanocytic abnormalities. Melanocytic cells are capable of producing melanin. When these cells retain the melanin that they have produced, they are referred to as continent melanocytes. When these melanocytes cells are deprived from the melanosomes or when they

---

\* Assistant Professor University of Dammam  
Consultant Ophthalmologist King Fahd Hospital  
Fellow Armed Forces Institute of Pathology  
Walter Reed Medical Army, Washington DC, USA  
King Fahd Hospital of the University  
Saudi Arabia  
Email: jalqahtany@yahoo.com

discharge melanin to adjacent epithelial cells, they are called incontinent melanocytes. Dermal, uveal and conjunctival melanocytes are derived from the neural crest and are solitary dendritic cells. The size, number, and melanin content of these cells tend to vary among different races<sup>1</sup>. Because differential diagnosis of these lesions is difficult, there is much confusion in the literature regarding its taxonomy.

The aim of this review is to update the readers' knowledge about conjunctival melanosis and its clinicopathologic classification.

## **METHOD**

Sequential review of titles, abstracts, and text from retrieved articles covering conjunctival melanosis from the early 1960 until the end of December 2012 was done.

## **RESULT AND DISCUSSION**

Conjunctival lesions that are derived from melanocytes can generate considerable clinical anxiety. The 10-year cumulative incidence of metastatic death from conjunctival melanoma was 32%<sup>2</sup>. Other conjunctival lesions that are pigmented do not actually represent proliferations of melanocytes; melanocytes may discharge melanin into squamous epithelial cells so that inclusion cysts, papillomas or squamous cell carcinomas may appear pigmented clinically<sup>3,4</sup>.

It is important to differentiate these types of lesion. Those with the lowest potential for malignancy are referred to as benign melanoses, which include complexion-associated melanosis, secondary melanosis, ephelis, and primary acquired melanosis (PAM) without atypia. In contrast, PAM with atypia is a transitional lesion, which if treated inadequately will progress to invasive malignant melanoma in 20% to 90% of cases, depending on the degree of atypia<sup>5</sup>.

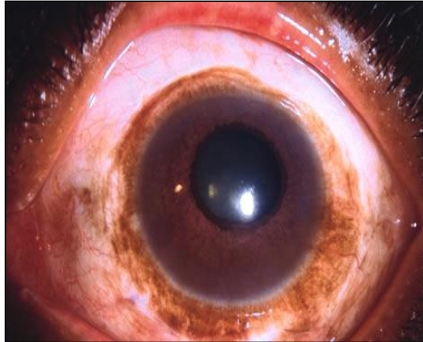
Melanocytic lesions of the conjunctiva are classified into congenital or acquired, epithelial or subepithelial and primary or secondary. Congenital melanosis is primary and they are divided into epithelial and subepithelial types. In contrast, acquired melanosis is epithelial and divided into primary and secondary. A good clinical history and a detailed clinical biomicroscopic examination of the eye and adnexa are essential for precise classification.

### **a) Epithelial Types**

Ephelides or freckles are flat, brown, patchy lesions that appear in portions of the skin that has been exposed to sun, and they tend to darken after such exposure. Most often they involve the bulbar conjunctiva near the limbus, but they may involve the bulbar or palpebral conjunctiva. The pigmented conjunctiva can move over the sclera. Ephelides are common in dark races and typically are present from birth or early childhood. The histology consists of increased pigmentation in the basal cell layer of the conjunctival epithelium; the number of melanocytes is normal or lower than normal. The melanocytes in an ephelis are not atypical and this lesion is not a precursor of malignant melanoma.

As its name implies, conjunctival complexion-associated melanosis is related to skin pigmentation. Individuals that are more heavily pigmented have a higher frequency of

conjunctival melanosis, and it tends to be more extensive in these patients than in less pigmented individuals, see figure 1. In black patients, the melanosis tends to be pigmented more deeply at the limbus and it then fans out, decreasing in intensity toward the fornix. It is usually bilateral, but may be asymmetric. Cases of complexion-associated melanosis rarely progress to a malignant melanoma.



**Figure 1: Complexion-Associated Melanosis in Non Caucasian Patient**

Conjunctival nevi are benign hamartomatous tumors composed of modified melanocytes named nevus cells derived embryologically from the neural crest. Although nevi are considered to be congenital lesions, they are often detected toward the end of the first decade of life. Apparent growth and increased pigmentation of conjunctival nevi is often caused by elevated levels of hormones during puberty or pregnancy, see figure 2a. Excisional biopsy is usually done for cosmetic reasons or when there is a concern about possible malignant transformation.

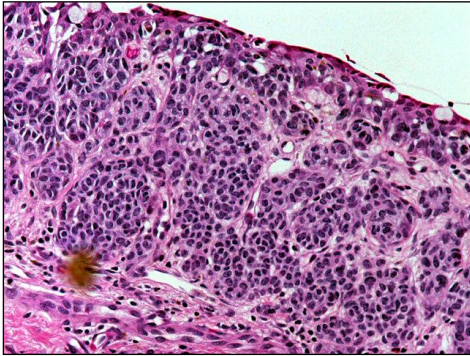


**Figure 2a: Pigmented Conjunctival Nevus in a Young Male Patient**

Conjunctival nevi are classified based on the location of the nevus in relation to the epithelium. The nevus cells are located at the epithelial-subepithelial junction in junctional nevi, whereas it is confined to the conjunctival stroma in subepithelial nevi. Most conjunctival nevi are compound nevi that have both junctional and subepithelial components. Junctional activity tends to decrease markedly with age. Junctional nevi are rare during childhood and do not occur in adults whereas subepithelial nevi are generally found in older adults<sup>6</sup>.

Microscopically, nevus cells often form aggregates called nests seen in lower magnification. Polarity may present, that is, more superficial nevus cells tend to be large, whereas cells

deeper in the stroma tend to be small, indicating aging of the nevi. Bland multinucleated nevoid giant cells are seen in some cases, see figure 2b.



**Figure 2b: Compound Nevus Contains Nevus Cells, at the Junction of Conjunctival Epithelium and in Subepithelial Tissue (H&E)**

Most compound conjunctival nevi are cystic and can be seen clinically with the slit lamp in some cases, an observation suggesting the diagnosis of these benign pigmented lesions.

### **b) Subepithelial Types**

Although the subepithelial types of congenital melanosis are not lesions of the conjunctiva, it is a differential diagnosis of pigmented conjunctival tumors owing to the fact that it is observed from the conjunctiva. The abnormal melanocytes are located in the sclera and episclera below the substantia propria of the conjunctiva.

#### **i) Congenital Ocular Melanocytosis (Melanosis Oculi)**

In congenital ocular melanocytosis, melanocytes fail to migrate to the epithelium and become entrapped within the soft tissues of the orbit, the meninges of the optic nerve, the eyelid dermis, the uvea, the sclera and the episclera. Clinically, the surface of the eye appears blue instead of brown or black as the case when lesions arise from conjunctival melanocytes. The blue color is due to the Tyndall effect because the brown melanin pigment is seen through a layer or layers of collagen in the episclera or sclera. The pigment appears spiculated and may surround lymphatic and blood vessels in the episclera. The pigmentation does not move with the conjunctiva. Although melanomas of the uveal tract and orbit have been reported in congenital melanosis oculi, pure conjunctival melanomas have not been described<sup>7,8</sup>.

A congenital increase in the number, size, and pigmentation of melanocytes of the uvea is associated with an increased number of pigmented melanocytes in the sclera and episclera. Congenital ocular melanocytosis is a unilateral condition and is more common among Caucasians.

#### **ii) Congenital Oculodermal Melanocytosis (Nevus of Ota)**

In this condition, the melanosis oculi is accompanied by ipsilateral melanosis of the deep dermal tissues of the lids or periocular skin or both. It is almost always unilateral and is more common among those of Asian or African descent. Associated findings in the involved eye include glaucoma, uveitis, and cataract.

Histologically, congenital oculodermal melanocytosis is associated with individual and small clusters of melanocytes that are interspersed with the connective tissue of the sclera, episclera, and dermis of the eyelid. Congenital oculodermal melanocytosis and congenital ocular melanocytosis (melanosis oculi) might be associated with melanosis of the orbital tissues, the meninges of the optic nerve or brain. Congenital oculodermal melanocytosis does predispose patients to malignant melanoma, especially among Caucasian patients. Malignant melanomas have been reported in the skin, conjunctiva, uvea, orbit, and even in the meninges.

## **Acquired Melanosis**

All cases of acquired melanosis are epithelial and they are divided into primary and secondary types.

### **Primary Acquired Melanosis (PAM)**

Previously, the terms precancerous melanosis, benign acquired melanosis, primary idiopathic acquired melanosis and intraepithelial melanocytic hyperplasia have been used for PAM<sup>1</sup>.

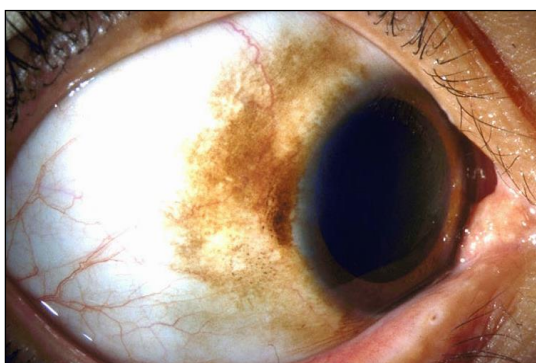
Reese was the first to classify PAM of the conjunctiva as either precancerous or cancerous melanosis on the basis of clinicopathological findings<sup>9</sup>. In his early comments, he remarked that many of these lesions evolved into malignant melanoma of the conjunctiva. He noted that this condition typically affected Caucasian patients and almost always corresponded to a unilateral diffuse brown pigmentation that moved with the conjunctiva over the sclera. The age of onset was approximately 40 to 50 years. In addition, Reese noted that 10% of eyes have conjunctival melanosis, which is most likely to be complexion-associated melanosis and he considered it to be congenital and his classification only applied to acquired melanosis.

Unfortunately, the classification of Reese led many ophthalmologists who wished to prevent the development of conjunctival melanoma to treat flat unilateral forms of conjunctival pigmentation aggressively and pathologists over diagnose cancerous melanosis. Subsequently, when Reese revised this condition, he found that only 17% of his patients who had been diagnosed with “precancerous” melanosis had developed conjunctival melanoma. In response to the overtreatment and incomplete understanding of this condition, Zimmerman proposed the term “benign acquired melanosis” rather than “precancerous melanosis” to emphasize that these lesions are histologically and cytologically benign and seldom progress to malignant melanoma, and unlike congenital melanosis oculi, they are acquired lesions<sup>10</sup>.

The term “benign acquired melanosis” encompassed a broad spectrum of histological changes, which included pigmentation of the conjunctival epithelium, melanocytic hyperplasia without atypia, and atypical melanocytic hyperplasia. Zimmerman proposed classifying the condition into two stages<sup>10</sup>. Stage I represented intraepithelial disease and was further sub-classified into stage IA (lesions in which there was little melanocytic atypia; melanocytic hyperplasia, if present, was confined to the lower layers of the epithelium) and stage IB (in which there was marked melanocytic hyperplasia). Stage I corresponded more or less to PAM with or without atypia, whereas stage II represented malignant melanoma. Stage IIA represented superficial invasion, and stage IIB represented deep invasion; the depth of invasion was not quantified.

WHO proposed “primary acquired melanosis” as a neutral non-judgmental term instead of “precancerous” or “benign acquired melanosis”<sup>1</sup>. The term “primary” was introduced to separate this condition from conjunctival pigmentation secondary to local disease (e.g., postinflammatory pigmentation), skin color (complexion-associated pigmentation), or systemic diseases (Addison's disease, neurofibromatosis or Peutz-Jeghers syndrome). The term “acquired” was retained from Zimmerman's classification to emphasize the differences between this condition and the blue episcleral and scleral pigmentation of congenital melanosis oculi<sup>10</sup>.

PAM of the conjunctiva is a unilateral flat brown pigmentation that is seen most commonly in Caucasian adults, middle-aged or older, see figure 3a. It is caused by the proliferation of melanocytes within the conjunctival epithelium. These lesions can be seen at any location on the conjunctiva, including the fornices and the tarsal conjunctiva. During the course of the disease, new areas of the conjunctiva might become involved while old lesions disappear.

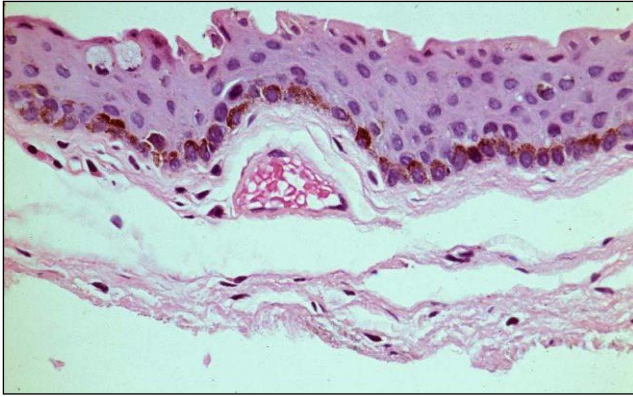


**Figure 3a: Primary Acquired Melanosis without Atypia, Flat Pigmented Lesion of the Conjunctiva which Developed in Adulthood**

PAM attracts a considerable amount of attention because it can transform into malignant melanoma of the conjunctiva. Unfortunately, it is impossible to predict clinically which lesions are most likely to become malignant. Shields et al reviewed 311 cases of PAM and found that as the extent of PAM in clock hours increased, the risk of transformation into melanoma also increased<sup>11</sup>. Also Shields et al found that melanoma arise from PAM (n=284; 74%), from pre-existing nevus (n=26; 7%), and de novo (n=72; 19%)<sup>12</sup>. The depth of color is an unreliable indication of histology: light tan lesions may contain atypical melanocytes, and some cases of PAM with atypia may be entirely non-pigmented clinically (acquired melanosis sine pigmento)<sup>13,14</sup>. Therefore, multiple biopsies from multiple sites are needed to assess the histopathological characteristics that predict malignancy. The risk of malignant change depends upon the features of the biopsies that can be observed under the microscope.

Histopathologically, PAM can be divided into two types: a) without cellular atypia and b) with cellular atypia. In lesions without cellular atypia, the melanocytes are restricted to the basement membrane of the epithelium; they retain their dendritic shape, and contribute pigment only to the surrounding basal and suprabasal epithelial cells, see figure 3b. However, PAM with atypia contains epithelioid cells and shows the spread of individual cells up toward the superficial epithelium in a pagetoid pattern.

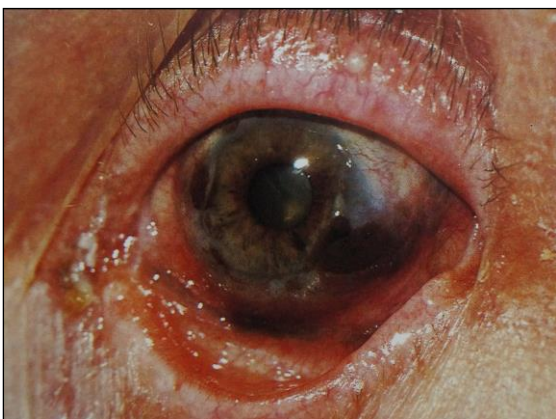




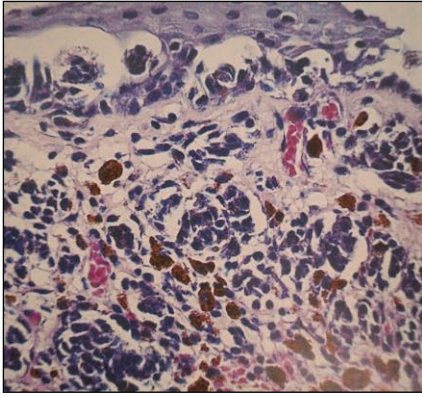
**Figure 3b: Primary Acquired Melanosis without Atypia. Hyperpigmentation of the Epithelium & Melanocytes Is Restricted to the Basement Membrane (H&E)**

### **Conjunctival Melanoma**

Malignant melanoma of the conjunctiva is a relatively rare malignancy. It accounted for 3% of the ocular cancers registered by the United States Veterans Administration from 1958 to 1964<sup>15</sup>. Approximately 75% of conjunctival melanomas arise from PAM with atypia, see figure 4a. The remainder arise de novo or from a preexisting nevus<sup>12</sup>. Usually, the lesion is nodular brown and well-vascularized, often with a large conjunctival feeding vessel. However, conjunctival melanomas **can be diffuse or nodular** and contain different cell types, which include spindle, polyhedral, epithelioid, and balloon cells, see figure 4b. These tumors do not typically invade the globe, but spread contiguously to invade the orbit directly. Systemic spread occurs through the lymphatic system.



**Figure 4a: Multiple Malignant Melanomas of the Conjunctiva Arising in Area of Primary Acquired Melanosis**



**Figure 4b: Malignant Melanoma Invading the Conjunctival Epithelium. (H&E)**

A crucial step in the management of conjunctival melanosis is the establishment of a correct diagnosis. Size, bilaterality, complexion, and the presence of an underlying condition that causes secondary melanosis are important parameters that can be used to differentiate PAM from non-neoplastic causes of conjunctival melanosis. When conjunctival melanoses contain thickened areas or are vascularized, these lesions may represent either an associated nevus or a malignant melanoma. If the thickened portion of the lesion corresponds to the initial manifestation or if it contains cystic epithelial inclusions, it is more likely to be a nevus. Bilaterality is the second parameter that distinguishes the lesions of PAM from complexion-associated melanosis. Complexion-associated pigmentations of the conjunctiva are often bilateral, whereas PAM occurs unilaterally. Complexion is important because patients with more darkly pigmented skin are unlikely to have PAM. Finally, the presence of an underlying disease which causes conjunctival pigmentation indicates a secondary type of melanosis rather than PAM.

The optimal treatment of conjunctival epithelial melanosis has not been determined. Conjunctival epithelial melanoses, which are small, flat and not inflamed are unlikely to be neoplastic and should be monitored without a biopsy. Biopsies should be taken for conjunctival melanoses in Caucasian patients if the lesion is progressive, not confined to the limbus and large. Any flat melanoses that become elevated or inflamed should also be biopsied. If the biopsy reveals a benign melanosis or PAM without atypia, follow-up is recommended. If it reveals PAM with atypia, then the entire involved conjunctiva should be treated<sup>16,17</sup>. The margins should be checked and all pigmented lesions in the palpebral conjunctiva should be excised. In addition to surgical excision, cryotherapy has been found to be effective in some cases of PAM with extensive atypical melanosis because melanocytes appear to be killed more easily by freeze-thaw than epithelial cells of the conjunctiva. In addition, topical chemotherapy with mitomycin has been found to be a good alternative to surgical excision and cryotherapy in the treatment of conjunctival PAM with atypia<sup>18-21</sup>.

Conjunctival melanomas disseminate by local extension and by spreading into regional lymph nodes. There is a great potential for hematogenous spread from the lymphatic system. Therefore, complete surgical excision with a clear margin of 4 mm, together with the removal of thin lamellar scleral flap from beneath the tumor and absolute alcohol treatment for the remaining sclera are recommended. Cryotherapy using a triple freeze-thaw technique is applied to the base of the lesion and conjunctival borders. Topical mitomycin C has been used after surgical excision and cryotherapy to treat residual disease. Exenteration of the orbit



is indicated for advanced disease when local excision or enucleation is insufficient to excise the tumor completely.

Factors predictive of death by multivariable analysis included tumor origin de novo ( $P < 0.001$ ), fornix location ( $P = 0.04$ ) and nodular tumor ( $P = 0.001$ )<sup>12</sup>.

## CONCLUSION

**Conjunctival melanosis presents a dilemma in diagnosis for the ophthalmologist. There is a mix-up in the clinical terminology for such lesions in the literature. Different classifications have been proposed for this entity through the last century. Review of the literature has been undertaken to clarify both the clinical spectrum of these lesions and the histopathological classification.**

---

**Potential conflicts of interest:** None.

**Competing interest:** None.    **Sponsorship:** None.

**Submission date:** 4 September 2013.    **Acceptance date:** 25 November 2013.

## REFERENCES

1. Harooni H, Schoenfield LR, Singh AD. Current Appraisal of Conjunctival Melanocytic Tumors: Classification and Treatment. *Future Oncol* 2011; 7(3): 435-46.
2. Kujala E, Tuomaala S, Eskelin S, et al. Mortality after Uveal and Conjunctival Melanoma: Which Tumour Is More Deadly? *Acta Ophthalmol* 2009; 87(2): 149-53.
3. Jahnle RL, Shields JA, Bernardino VB Jr, et al. Conjunctival Inclusion Cyst Simulating Malignant Melanoma. *Am J Ophthalmol* 1985; 100(3): 483-4.
4. Shields CL, Manchandia A, Subbiah R, et al. Pigmented Squamous Cell Carcinoma in Situ of the Conjunctiva in 5 Cases. *Ophthalmology* 2008; 115(10): 1673-8.
5. Novais GA, Fernandes BF, Belfort RN, et al. Incidence of Melanocytic Lesions of the Conjunctiva in a Review of 10675 Ophthalmic Specimens. *Int J Surg Pathol* 2010; 18(1): 60-3.
6. Jakobiec FA, Folberg R, Iwamoto T. Clinicopathologic Characteristics of Premalignant and Malignant Melanocytic Lesions of the Conjunctiva. *Ophthalmology* 1989; 96(2): 147-66.
7. Yanoff M, Zimmerman LE. Histogenesis of Malignant Melanomas of the Uvea. 3. The Relationship of Congenital Ocular Melanocytosis and Neurofibromatosis to Uveal Melanomas. *Arch Ophthalmol* 1967; 77(3): 331-6.
8. Hagler WS, Brown CC. Malignant Melanoma of the Orbit Arising in a Nevus of Ota. *Trans Am Acad Otolaryngol* 1966; 70(5): 817-22.
9. Reese AB: Precancerous and Cancerous Melanosis. *Am J Ophthalmol* 1966; 61(5 Pt 2): 1272-7.
10. Zimmerman LE. Criteria for Management of Melanosis. *Arch Ophthalmol* 1966; 76(2): 307-8.
11. Shields JA, Shields CL, Mashayekhi A, et al. Primary Acquired Melanosis of the Conjunctiva: Experience with 311 Eyes. *Trans Am Ophthalmol Soc.* 2007; 105: 61-71.

12. Shields CL, Markowitz JS, Belinsky I, et al. Conjunctival Melanoma: Outcomes Based on Tumor Origin in 382 Consecutive Cases. *Ophthalmology* 2011; 118(2): 389-95.
13. Zembowicz A, Mandal RV, Choopong P. Melanocytic Lesions of the Conjunctiva. *Arch Pathol Lab Med* 2010; 134(12): 1785-92.
14. Griffith WR, Green WR, Weinstein GW. Conjunctival Malignant Melanoma Originating in Acquired Melanosis Sine Pigmento. *Am J Ophthalmol* 1971; 72(3): 595-9.
15. Keller AZ. Histology, Survivorship and Related Factors in the Epidemiology of Eye Cancers. *Am J Epidemiol* 1973; 97(6): 386-93.
16. Damato B, Coupland SE. Management of Conjunctival Melanoma. *Expert Rev Anticancer Ther* 2009; 9(9): 1227-39.
17. Shildkrot Y, Wilson MW. Conjunctival Melanoma: Pitfalls and Dilemmas in Management. *Curr Opin Ophthalmol* 2010; 21(5): 380-6.
18. Kim JW, Abramson DH. Topical Treatment Options for Conjunctival Neoplasms. *Clin Ophthalmol* 2008; 2(3): 503-15.
19. Schallenberg M, Niederdräing N, Steuhl KP, et al. Topical Mitomycin C as a Therapy of Conjunctival Tumours. *Ophthalmologe* 2008; 105(8): 777-84.
20. Anandajeya WV, Corrêa ZM, Augsburger JJ. Primary Acquired Melanosis with Atypia Treated with Mitomycin C. *Int Ophthalmol* 2009; 29(4): 285-8.
21. Russell HC, Chadha V, Lockington D, et al. Topical Mitomycin C Chemotherapy in the Management of Ocular Surface Neoplasia: A 10-Year Review of Treatment Outcomes and Complications. *Br J Ophthalmol* 2010; 94(10): 1316-21.