CASE REPORTS

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Conjunctival melanocytic tumors in children – a challenge in diagnosis and treatment

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Abstract

Conjunctival melanocytic lesions are very diverse pigmented tumors that include benign, premalignant and malignant tumors. The aim of this article is to highlight the clinical and histopathological aspects of conjunctival melanocytic tumors at children. This study is a retrospective case series study of three patients selected from fifteen cases with melanocytic conjunctival tumors who were operated in the Department of Ophthalmology, "St. Spiridon" Emergency Hospital, Iaşi, Romania. A systematic review of the literature was undertaken, using an electronic search of *PubMed/MEDLINE*, *Google Scholar* and *ISI Web of Knowledge*, to identify original English or French articles and reviews on this subject. Patients were diagnosed by the same doctor between 2004 and 2016, in ambulatory of Department of Ophthalmology of the same Hospital. The age of patients was between 7 and 17 years old. Three cases (boys) were treated by surgery – one patient with conjunctival malignant melanoma (histologically confirmed) derived from a pre-existing benign conjunctival nevus (diagnosed 1.5 years before), a patient was operated for aesthetic reasons (with histological diagnosis of compound conjunctival melanocytic nevus) and one boy was diagnosed of melanocytic conjunctival nevus. All cases operated had normal visual acuity and fundoscopy. There was no regional lymph node present in any case studied. The traditional method for clinical diagnosis of suspected pigmented conjunctival lesions was to remove these lesions surgically and to examine architectural and cytological features with light microscopy. We recommend an immunohistochemical staining for the detection of specific cellular antigens in conjunctival melanocytic tumors in children. The diagnosis, treatment and the follow-up of the patient were challenges for the ophthalmologist.

***Keywords*:** conjunctival nevus, conjunctival malignant melanoma, primary acquired melanosis, immunohistochemical tests.

Introduction

Melanocytic proliferations are the most common tumors of the conjunctiva, accounting for up to 53% of all conjunctival neoplasms [1]. Conjunctival melanocytic lesions are represented by a wide range of pigmented tumors that include benign, premalignant and malignant tumors. Conjunctival nevi are the most common pigmented tumors (more than 50%) and are typically found in the interpalpebral bulbar conjunctiva [2]. Other conjunctival melanocytic lesions are melanosis (conjunctival and acquired) [1–3]. Conjunctival melanoma may arise *de novo* (12–26%), or from primary acquired melanosis (10–74%) [4, 5]. With a prevalence of one per two million people of European ancestry, malignant conjunctival melanoma accounts for 1–2% of all eye malignancies and 5% of all ocular melanoma [1, 2, 5]. Most frequently, it appears in middle aged to elderly persons with a peak incidence in the fifth decade of life [6]. In childhood and adolescence, conjunctival melanocytic nevi are common [1–3], while the conjunctival melanoma is extremely rare in children [7, 8].

Melanocytic proliferations are often challenging lesions for the pathologist who is not familiar with the unique histological features of melanocytic proliferations in this location and with the nomenclature used by the ophthalmologist [1].

The traditional method for clinical diagnosis of suspected pigmented conjunctival lesions has been to remove these lesions surgically and to examine the architectural and cytological features with light microscopy. An immunohistochemical (IHC) staining is recommended for the detection of specific cellular antigens [9].

Ophthalmologists monitor benign conjunctival tumors annually, since adulthood, because nevi can be confused with melanomas, and epithelial or stromal lesions with carcinomas. For children and teenagers, surgery is recommended only when growth or functional problems are observed [10].

There are studies showing that conjunctival melanomas share molecular abnormalities with cutaneous melanomas [11–13]. They also associate with refractive amblyopia and an early ophthalmological screening is needed in all children with pigmented conjunctival lesions to be able to prevent refractive amblyopia [14]. In establishing the diagnosis and the line of treatment, these cases were a permanent challenge for the entire team, ophthalmologist, pediatric doctor, pathologist and ocular surgeon.

The aim of this article is to highlight the clinical and histopathological aspects of conjunctival melanocytic tumors at children.

This study presented a retrospective case series of three patients (all males) with melanocytic conjunctival tumors. Patients were diagnosed and surgically treated by the same doctor between 2004 and 2016, in the Outpatient Clinic of the Department of Ophthalmology, "St. Spiridon" Emergency Hospital, Iaşi, Romania. We selected for

presentation three children with some particularities in diagnosis and treatment of conjunctival melanocytic tumors. All cases had normal visual acuity and no other anterior or posterior ocular modifications. There were no regional lymph nodes in all cases studied. Clinical parameters observed: onset of pigmentary conjunctival lesions, diameter and color of the lesion, type of histological examinations, and follow-up of the conjunctival scar after treatment, the presence of lymph nodes. All cases were histologically analyzed in the Department of Pathology of the same Hospital. The traditional method for clinical diagnosis of suspected pigmented conjunctival lesions was to remove these lesions surgically and to examine architectural and cytological features with light microscopy. An IHC staining was recommended for the detection of specific cellular antigens.

Case presentations

Case No. 1

The patient C.P., a white 7-year-old boy, from a local orphanage house, was examined in the Eye Clinic, "St. Spiridon" Emergency Hospital, Iaşi, Romania. Boy's pediatrician observed the lesion since he came with a pigmented tumoral mass located on the bulbar conjunctiva of the right eye. The time and circumstances of appearance of lesion are uncertain (the history is confusing, with possibility of a pre-existing minor, non-penetrating ocular trauma). The lesion was present 1.5 years before (when the pediatrician begun working in that orphanage house) but since that moment the size and amount of pigmentation increased. At the time of first visit examination showed a non-tender, solitary, sharply demarcated, slightly prominent pigmented mass, oval in shape, of 5.3×3 mm, with irregular borders and multi-microcystic spaces within the substance, giving rise to a multi-microgranulary formation, which moved freely over the globe. The lesion was located 3 mm from the corneal limbus in the temporal bulbar conjunctiva of the right eye. The lesion was accompanied by dilated episcleral feeding vessels (Figure 1, a and b). Otherwise, anterior segment examination and fundoscopy in both eyes revealed no other pathology. Visual acuity was 20/20 in both eyes and B-scan ultrasonography was normal. No lymph nodes were present. The conjunctival mass was excised along with at least 1 mm of apparently normal tissue and together with underlying Tenon's capsule, followed by cryotherapy over the underling sclera. The local defect resulted after excision was covered with an autologous rotational conjunctival graft. The specimen was sent to the Laboratory of Pathology, which revealed a proliferation of round and polygonal cells confined to nests or in a diffuse pattern, with low cytoplasmic content and hyperchromatic nuclei. The proliferation partly infiltrated the superficial epithelium. In the subepithelial region, the large nest distribution prevailed and the cells were more homogenous, with less pigmented nuclei. There were also present small cystic spaces delimitated by proliferating cells (Figure 2, a and b). No difference could be made between malignant conjunctival melanoma and benign conjunctival nevus. A special IHC technique was performed in order to stain human melanoma black-45 (HMB-45) monoclonal antibody that is characteristic for malignant conjunctival melanoma (Figure 3, a and b). The reaction was positive at the level of subepithelial cells arranged in nests and in cells that infiltrated the epithelium and negative at the level of profound cells of the proliferation (which represented a nevus structure). It became obvious that we dealt with a conjunctival melanoma with lateral spread, developed from a pre-existing nevus. After 36 months, it was only a sub-conjunctival scar on temporal bulbar conjunctiva, with no other modifications of conjunctiva.

Case No. 2

The patient S.A., a white 17-year-old boy, was examined in the Eye Clinic, "St. Spiridon" Emergency Hospital, Iaşi, Romania. Boy's parents observed the lesion on the left eye a pigmented tumoral mass on the bulbar conjunctiva. Visual acuity and fundoscopy was normal. No lymph nodes were present. At the time of his first visit, a non-tender, solitary, sharply demarcated, slightly prominent pigmented mass, oval in shape, of 6×2.5 mm, with irregular borders could be noticed, which could move freely over the globe (Figure 4).

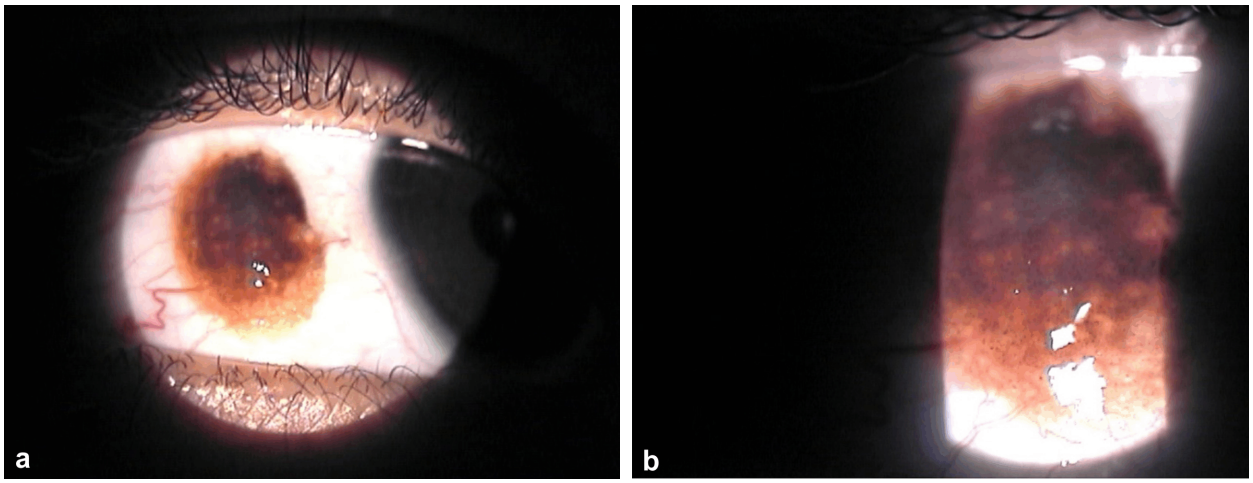

Figure 1 – ***(a) Solitary, sharply demarcated, unevenly pigmented mass, located 3 mm from the corneal limbus in the temporal conjunctiva of the right eye with dilated episcleral feeding vessels (slit lamp photography). (b) Lesion is prominent and pigmentation is variable, with microcystic spaces within the substance.***

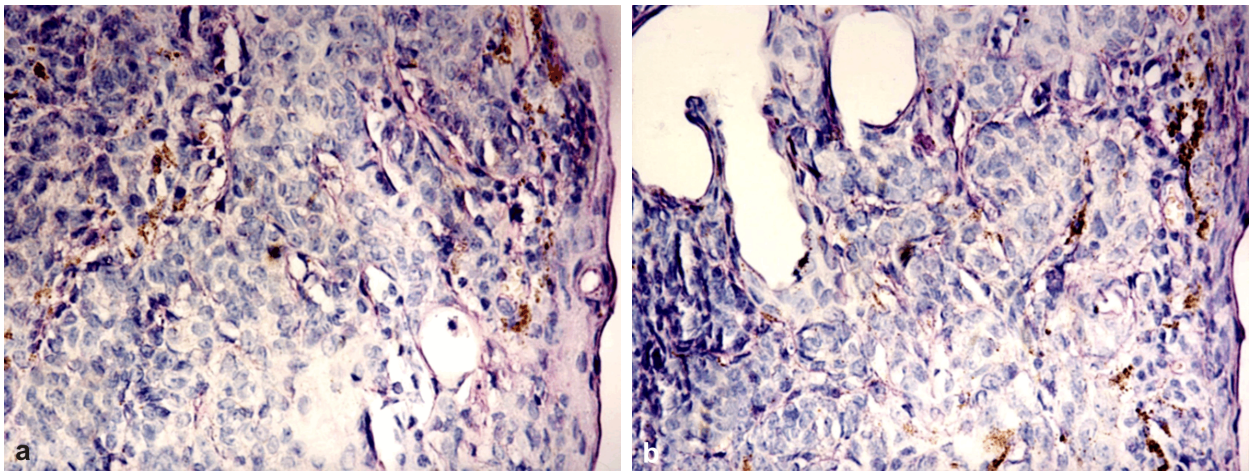

Figure 2 – ***(a and b) The tumor is composed of a proliferation of round and polygonal cells confined to nests or in a diffuse pattern with low citoplasmatic content and hipercromatic nuclei, infiltrating the superficial layer. In the subepithelial region, the large nest distribution prevailed and the cells were more homogenous, with less pigmented nuclei. Small cystic spaces are outlined by proliferating cells. Hematoxylin–Eosin (HE) staining, ×400.***

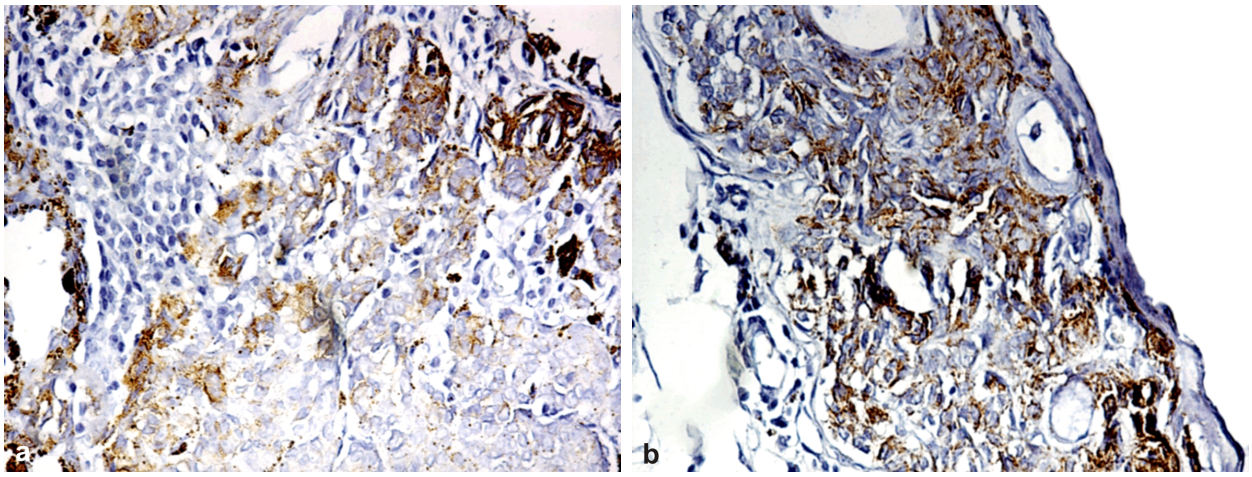

Figure 3 – ***(a and b) Immunohistochemical staining positive at the level of subepithelial cells and in cells that infiltrated the epithelium and negative at the level of profound cells of the proliferation. Anti-HMB-45 antibody immunostaining, ×400. HMB-45: Human melanoma black-45.***

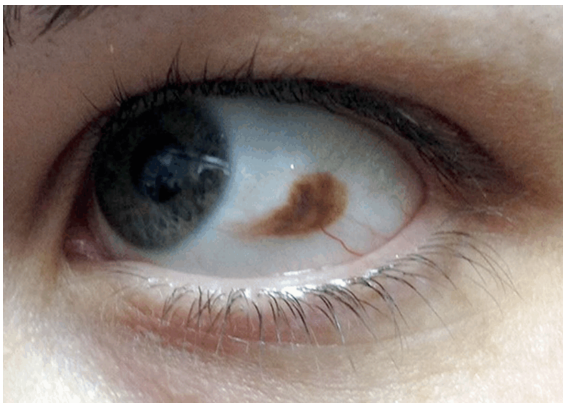

Figure 4 – ***Conjunctival melanocytic nevus (gross photography, left eye).***

The lesion was the same since the boy or parents observed the conjunctival pigmentation. The lesion was located in the temporal bulbar conjunctiva of the left eye. The lesion was accompanied by dilated episcleral feeding vessels. The boy and the parents wanted it operated only for aesthetic reason. The conjunctival lesion was excised in normal tissues. The histological diagnosis was compound conjunctival melanocytic nevus. The post-operative evolution was normal, and the scar from bulbar conjunctiva is small and without other modification.

Case No. 3

The patient M.A., a white 9-year-old boy, was examined in the Eye Clinic, "St. Spiridon" Emergency Hospital, Iaşi, Romania. We observed a temporal pigmented lesion (3×2 mm) near the corneal limbus (at 1 mm). The patient told us that the lesions were there since birth but he noticed that it increased in the last year (Figure 5, a and b). Visual acuity and fundoscopy were normal. No lymph nodes were present. We operated the patient and the histological exam established that the lesion is a conjunctival melanocytic compound nevus (Figure 6, a and b). The excision was completed in normal tissue.

Discussions

The diagnosis for first case was difficult because of confused history and lack of data concerning the tumor's circumstances of appearance (we do not know if the pigmentation was present at birth). The presumed trauma

would raise suspicion of a pyogenic granuloma; this lesion appears frequently after surgery or trauma. Difficult was also the differentiation between benign nevus [8] and malignant melanoma.

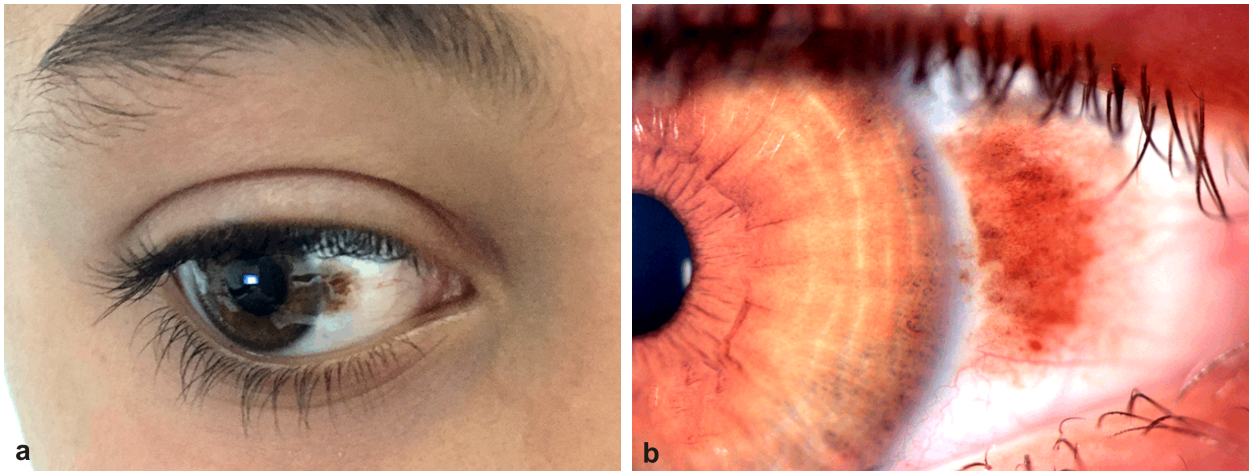

Figure 5 – ***(a) Pigmented mass located 1 mm from corneal limbus in the temporal conjunctiva of the right eye with dilated episcleral feeding vessels. (b) The lesion is not prominent and pigmentation is variable (gross photography at slit lamp, right eye).***

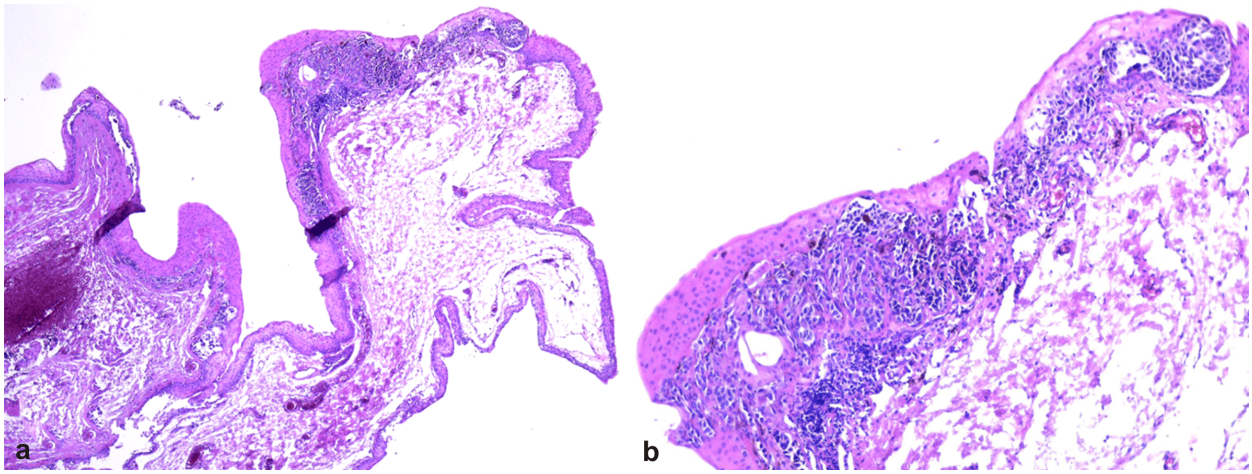

Figure 6 – ***(a) Conjunctival fragment with melanocytic subepithelial and junctional proliferation. (b) Melanocytic cells have intracytoplasmatic melatonin. HE staining: (a) ×40; (b) ×100.***

The clinical elements for positive diagnosis are: (*i*) young age (presentation of conjunctival nevus is usually during puberty or early adult life and melanoma presents typically during the early fifties; the tumor is extremely rare during the first two decades of life), (*ii*) the solitary, well demarcated lesion, (*iii*) free movement over episclera and (*iv*) the uneven pigmentation and microcystic appearance of the lesion. For the latter were suggestive: prominent aspect and increasing in size and amount of pigmentation.

Conjunctival malignant melanoma is a rare ocular malignancy [15]. It occurs in the following pathological forms: melanoma with primary acquired melanosis (50–70%), melanoma arising from a pre-existing nevus (20%) [16] or *de novo*. In rare cases, an underlying ciliary body melanoma may extend through the scleral emissary vessels and produce a dark epibulbar mass. Hardly ever a malignant melanoma may extend from eyelids to conjunctiva. A common site is the limbic area and bulbar conjunctiva but any other location on the conjunctiva is possible. The usual clinical aspect is a solitary nodule with variable pigmentation and heavy vascularization that may become fixed to episclera.

IHC studies made the differential diagnosis for different types of conjunctival melanocytic nevi [9]. The IHC exam was highly relevant for our first presented case.

The behavior of conjunctival melanoma remains unpredictable: some may grow in a nodular fashion and some may invade the globe and extend posterior to the orbit, causing one-sided proptosis, which can be confused with extraocular manifestations of the endocrinological diseases as well as other intraorbital tumors [17, 18].

The outcome is partly determined by the site involved: bulbar conjunctival melanomas have a better prognosis then melanomas of the palpebral conjunctiva, fornix or caruncle. Although they may metastasize, they have a better prognosis then melanoma of the eyelids skin.

Cytological risk factors for recurrence and metastasis are large size, multicentricity, extralimbal tumors involving the caruncle, fornix or palpebral conjunctiva, epithelioid cell type, lymphatic invasion or orbital spread and evidence of extension to the margins of excision [6]. In adults, tumor thickness has strong prognostic implications in adults: thin lesions with 0.75 mm or less have a survival rate of 100%, while thicker lesions with 3 mm or more have only a 22% survival rate [9].

An excision biopsy should be considered for any suspicious pigmented epibulbar lesion since this procedure does not seem to increase the risk of metastasis [19]. Treatment usually consists of complete local excision (supplemented with cryotherapy to the conjunctival margins and bare sclera [20, 21]. Excision and cryotherapy are used as treatment for conjunctival melanoma and primary acquired melanosis with atypia. Recurrences are typically associated with incomplete excision, corneal involvement and multifocal disease [22, 23]. Diffuse melanoma is treated by excision of localized nodules and cryotherapy or Mitomycin C to the diffuse component. Orbital recurrences and lymph node involvement are treated by local resection and radiotherapy. Melanic tumors are resistant to X-rays, but not to Cobalt or Radium [24]. Exenteration does not improve the survival rate and is therefore reserved for patients with extensive and aggressive tumors [25, 26].

For cases two and three the diagnosis were from the beginning a benign tumor and the postoperative evolution was very good. Inflammatory conjunctival nevi can be in association with allergic conjunctivitis, and despite of periods of rapid growth, there are histologically benign tumors [26].

Conjunctival lesions can be associated with refractive amblyopia, if ophthalmological examination is too late. The treatment for melanocytic lesions will be surgery when growth or functional problems are observed. Early ophthalmological screening for children can prevent refractive amblyopia and can improve the quality of life and, all pigmented conjunctival lesions need monitoring [14, 27].

It is difficult to extrapolate information regarding adult conjunctival melanoma to children because conjunctival melanoma is extremely rare in children. In such instances, a conjunctival nevus can undergo malignant transformation into melanoma [22]. IHC studies for melanocytic markers, such as HMB-45 and melanoma-associated antigen recognized by T cells-1 (MART-1) may help in the differential diagnosis of small round blue cell tumors in the conjunctiva. However, immunohistochemistry plays a limited role in differential diagnosis between benign and malignant conjunctival lesions [1, 28, 29]. A newer non-invasive technology currently being tested on histo-pathological specimens of conjunctival melanocytic lesions uses patterns of pigment chemistry [30].

After a full ophthalmic examination, a complete physical examination, including palpation of the parotid, preauricular, submandibular, and cervical lymph nodes should be done [31]. The common sites of conjunctival melanoma metastasis are regional lymph nodes, brain, lungs and liver [32]. Any suspicious lesion found at the eye level requires early diagnosis and surgical excision in order to prevent the invasion of the eyeball and of the eye socket with loss of visual acuity [33].

Treatment of conjunctival-pigmented lesions consists in surgery, cryotherapy [34], adjuvant chemotherapy [35], use of Mitomycin C [36] and topical Interferon-α-2B [37]. Future directions in topical chemotherapy agents are 5-Fluorouracil (5-FU) [38], Cisplatin [39] and Bortezomib [40]. The defect remaining after the excision of the tumor found at the conjunctiva level can be repaired through conjunctivoplasty or amniotic membrane transplant [41]. Patients with pigmented conjunctival lesions should be monitored for ocular scars and also for other systemic diseases.

Conclusions

The diagnosis and treatment of conjunctival melanocytic lesions are a challenge for the ophthalmologist because the patient does not know if the lesion increased or not. Often, patients want to be operated only for aesthetic reasons. It can be associated with refractive amblyopia, if ophthalmological examination is too late. Treatment of melanocytic lesions will be surgery when growth or functional problems are observed. Evolution after surgery in normal tissue is very good.

Conflict of interests

The authors do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of the manuscript.

References

[1] Zembowicz A, Mandal RV, Choopong P. Melanocytic lesions of the conjunctiva. Arch Pathol Lab Med, 2010, 134(12): 1785–1792.

[2] Harooni H, Schoenfield LR, Singh AD. Current appraisal of conjunctival melanocytic tumors: classification and treatment. Future Oncol, 2011, 7(3):435–446.

[3] Costea CF, Turliuc MD, Dimitriu G, Bogdănici CM, Moţoc A, Chihaia MA, Dancă C, Cucu A, Cărăuleanu A, Dumitrescu N, Indrei L, Turliuc Ş. Inflammatory juvenile compound conjunctival nevi. A clinicopathological study and literature review. Rom J Morphol Embryol, 2017, 58(3):739–747.

[4] Mudhar HS, Rennie IG. Local conjunctival metastasis from primary conjunctival melanoma: clinico-pathological correlation and implications. Br J Ophthalmol, 2013, 97(1):33–39.

[5] Kenawy N, Lake SL, Coupland SE, Damato BE. Conjunctival melanoma and melanocytic intra-epithelial neoplasia. Eye (Lond), 2013, 27(2):142–152.

[6] Shields CL, Shields JA, Gündüz K, Cater J, Mercado GV, Gross N, Lally B. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Arch Ophthalmol, 2000, 118(11):1497–1507.

[7] Brownstein S, Faraji H, Jackson WB, Font RL. Conjunctival melanoma in children: a clinicopathologic study of 2 cases. Arch Ophthalmol, 2006, 124(8):1190–1193.

[8] Gomi CF, Robbins SL, Heichel CW, Gross RD, Granet DB. Conjunctival diseases. In: Nelson LB, Olitsky SE (eds). Harley's pediatric ophthalmology. 5th edition, Lippincott Williams & Wilkins, 2005, Chapter 11, 201–216.

[9] Jacobiec FA, Colby K, Bajart AM, Saragas SJ, Moulin A. Immunohistochemical studies of atypical conjunctival melanocytic nevi. Arch Ophthalmol, 2009, 127(8):970–980.

[10] Maschi C, Caujolle JP, Liolios I, Costet C. [Benign conjunctival tumors]. J Fr Ophthalmol, 2013, 36(9):796–802.

[11] Vajdic CM, Hutchins AM, Kricker A, Aitken JF, Armstrong BK, Hayward NK, Armes JE. Chromosomal gains and losses in ocular melanoma detected by comparative genomic hybridization in an Australian population-based study. Cancer Genet Cytogenet, 2003, 144(1):12–17.

[12] Van Raamsdonk CD, Bezrookove V, Green G, Bauer J, Gaugler L, O'Brien JM, Simpson EM, Barsh GS, Bastian BC. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature, 2009, 457(7229):599–602.

[13] Van Raamsdonk CD, Griewank KG, Crosby MB, Garrido MC, Vemula S, Wiesner T, Obenauf AC, Wackernagel W, Green G, Bouvier N, Sozen MM, Baimukanova G, Roy R, Heguy A, Dolgalev I, Khanin R, Busam K, Speicher MR, O'Brien J, Bastian BC. Mutations in GNA11 in uveal melanoma. N Engl J Med, 2010, 363(23):2191–2199.

[14] Bogdănici ST, Costin D, Bogdănici CM. Quality of life for amblyopic children and their parents. Rev Med Chir Soc Med Nat Iaşi, 2015, 119(1):214–220.
[15] Fasina O, Oluwasola OA. Conjunctival melanoma in South-western Nigeria: a case series and review of literature. Int Ophthalmol, 2017 Jun 19.
[16] Seregard S. Conjunctival melanoma. Surv Ophthalmol, 1998, 42(4):321–350.
[17] Buzdugă CM, Costea CF, Dumitrescu GF, Turliuc MD, Bogdănici CM, Cucu A, Dumitrescu N, Indrei L, Şapte E, Ciobanu Apostol DG. Cytological, histopathological and immunological aspects of autoimmune thyroiditis: a review. Rom J Morphol Embryol, 2017, 58(3):731–738.
[18] Strianese D, Piscopo R, Elefante A, Napoli M, Comune C, Baronissi I, Liuzzi R, Ferrara M, D'Alessandro A, Ruggiero P, Napolitano P, Grassi P, Iuliano A, Russo C, Brunetti A, Bonavolontà G. Unilateral proptosis in thyroid eye disease with subsequent contralateral involvement: retrospective follow-up study. BMC Ophthalmol, 2013, 13:21.
[19] Grecu PI, Stefanescu-Dima A, Ursea L, Stoica C. Tumori conjunctivale pigmentate la copii: analiza deciziei chirurgicale. Oftalmologia, 2003, 56(1):27–32.
[20] Shields CL, Shields JA. Tumors of the conjunctiva and cornea. Surv Ophthalmol, 2004, 49(1):3–24.
[21] Strempel I, Kroll P. Conjunctival malignant melanoma in children. Ophthalmologica, 1999, 213(2):129–132.
[22] Paridaens AD, Minassian DC, McCartney AC, Hungerford JL. Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathologic study of 256 cases. Br J Ophthalmol, 1994, 78(4):252–259.
[23] Shields CL, Naseripour M, Shields JA, Eagle RC Jr. Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid sebaceous gland carcinoma. Ophthalmology, 2001, 109(11): 2129–2133.
[24] Tiutiuca C, Voicu D, Brujbu I, Macovei L, Ciupilan C, Bogdanici C, Bulimar V. Malignant tumors of the eyeball and its appendixes. Rev Chim, 2016, 67(8):1641–1645.
[25] Papandroudis AA, Dimitrakos SA, Stangos NT. Mitomycin C therapy for conjunctival-corneal intraepithelial neoplasia. Cornea, 2002, 21(7):715–717.
[26] Missotten GS, Keijser S, de Keizer RJ, de Wolff-Rouendaal D. Conjunctival melanoma in the Netherlands: a nationwide study. Invest Ophthalmol Vis Sci, 2005, 46(1):75–82.
[27] Bogdanici ST, Martinescu G, Sandulache CM, Bogdanici CM. Socio-professional integration for amblyopic patients. Revista de Cercetare şi Intervenţie Socială, 2016, 52:187–194.
[28] Sharara NA, Alexander RA, Luthert PJ, Hungeriord JL, Cree IA. Differential immunoreactivity of melanocytic lesions of the conjunctiva. Histopathology, 2001, 39(4):426–431.
[29] Vora GK, Demirci H, Marr B, Mruthyunjaya P. Advances in the management of conjunctival melanoma. Surv Ophthalmol, 2017, 62(1):26–42.
[30] Westekemper H, Karimi S, Süsskind D, Anastassiou G, Freistühler M, Steuhl KP, Bornfeld N, Schmid KW, Grabellus F. Expression of HSP 90, PTEN and Bcl-2 in conjunctival melanoma. Br J Ophthalmol, 2011, 95(6):853–858.
[31] Grove AS Jr. Melanomas of the conjunctiva. Int Ophthalmol Clin, 1980, 20(2):161–175.
[32] Kurli M, Chin K, Finger PT. Whole-body 18 FDG PET/CT imaging for lymph node and metastatic staging of conjunctival melanoma. Br J Ophthalmol, 2008, 92(4):479–482.
[33] Turliuc MD, Sava A, Dumitrescu GF, Cucu A, Eşanu A, Tudorache C, Costache II, Costea CF. Right visual loss due to choroidal metastasis of a papillary adenocarcinoma of the lung: a case report. Rom J Morphol Embryol, 2015, 56(3): 1173–1177.
[34] Layton C, Glasson W. Clinical aspects of conjunctival melanoma. Clin Exp Ophthalmol, 2002, 30(2):72–79.
[35] Rodríguez-Ares T, Touriño R, De Rojas V, Becerra E, Capeans C. Topical mitomycin C in the treatment of pigmented conjunctival lesions. Cornea, 2003, 22(2):114–117.
[36] Kurli M, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience. Graefes Arch Clin Exp Ophthalmol, 2005, 243(11):1108–1114.
[37] Herold TR, Hintschich C. Interferon alpha for the treatment of melanocytic conjunctival lesions. Graefes Arch Clin Exp Ophthalmol, 2010, 248(1):111–115.
[38] Kim JW, Abramson DH. Topical treatment options for conjunctival neoplasms. Clin Ophthalmol, 2008, 2(3):503–515.
[39] Hamaï A, Richon C, Meslin F, Faure F, Kauffmann A, Lecluse Y, Jalil A, Larue L, Avril MF, Chouaib S, Mehrpour M. Imatinib enhances human melanoma cell susceptibility to TRAIL-induced cell death: relationship to Bcl-2 family and caspase activation. Oncogene, 2006, 25(58):7618–7634.
[40] Amiri KI, Horton LW, LaFleur BJ, Sosman JA, Richmond A. Augmenting chemosensitivity of malignant melanoma tumors *via* proteasome inhibition: implication for bortezomib (VELCADE, PS-341) as a therapeutic agent for malignant melanoma. Cancer Res, 2004, 64(14):4912–4918.
[41] Şapte E, Costea CF, Cărăuleanu A, Dancă C, Dumitrescu GF, Dimitriu G, Chihaia MA, Buzdugă CM, Cucu A, Turliuc MD. Histological, immunohistochemical and clinical considerations on amniotic membrane transplant for ocular surface reconstruction. Rom J Morphol Embryol, 2017, 58(2):363–369.

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