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Conjunctival melanoma in children: a systematic review

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Abstract
Introduction and Objective: Conjunctival melanoma (CM) is rare, particularly in children. It’s characterized by high aggressiveness and a tendency to metastasize. Due to the limited number of published case reports and studies in the pediatric population, it’s difficult to standardize diagnostic and therapeutic procedures. The aim of this paper is to collect and systematize the available information on cases of conjunctival melanoma in children.

Materials and Methods: Two databases were used for the review: PubMed and Scopus. Additionally, references were manually searched. After removing duplicates, 283 articles were obtained, of which 20 were included in the review. The analysis included articles in English that contained detailed information on the course of CM in children.

Abbreviated Description of the State of Knowledge: Conjunctival melanoma accounts for 2-5% of all eye tumors. Clinically, it presents as a pigmented lesion with heterogeneous shape and structure. Its development may be associated with UV radiation and genetic mutations. In diagnostic process, an ophthalmological examination is crucial, along with the search for potential metastases and recurrences. Treatment primarily involves surgical removal, with the addition of cryotherapy, chemotherapy, and radiotherapy if necessary.

Summary: Despite rare occurrence of CM, due to its high aggressiveness, every conjunctival lesion should be thoroughly examined with oncological vigilance. The amount of data on this subject is limited, so further research is needed to help develop prognosis and management strategies. A greater number of studies in the future may also contribute to the development of new therapeutic options, thereby improving outcomes.

Introduction

Conjunctival melanoma (CM) is a rare, aggressive disease. It's well known to metastasize to regional lymph nodes [1]. The incidence of CM increases with age, being more frequent among older individuals. The average age at diagnosis ranging from 55 to 65 years. It is extremely rare in individuals under 20 years old, accounting for only 1% of conjunctival melanoma cases [1, 2].

In the pathogenesis of CM, genetic mutations in the MAPK and PI3K/AKT/mTOR pathways, as well as telomere dysfunction, are considered [3]. The role of UV radiation in the development of CM remains controversial [2].

Conjunctival melanoma most commonly presents as a conjunctival lesion with a color ranging from light to dark brown. Rarely, the lesion may be amelanotic [2].

The prognosis depends on many factors including the underlying condition on which the lesion developed, its location, color, and histological type [2, 4, 5].

The aim

We decided to conduct this systematic review aiming to collect and systematize available information about conjunctival melanoma in children considering detailed information about the course of each case found.

Abbreviated Description of the State of Knowledge

Conjunctival anatomy

The conjunctiva is a mucous membrane composed of stratified squamous epithelium covering the limbal region, columnar epithelium covering the fornix area and fibrovascular stroma. It covers the posterior surface of the eyelid (palpebral portion), the fornix (forniceal portion), the surface of the eyeball (bulbar portion) and the corneoscleral limbus (limbal portion). Special regions of the conjunctiva include the plica semilunaris and the caruncle [6].

Conjunctival tumors can develop from both the epithelium and stroma and their clinical and histopathological characteristics are like those of other mucous membrane-derived tumors [6].

Epidemiology

Conjunctival melanoma is an uncommon condition. It constitutes 2%–5% of all eye tumors and 5%–7% of all ocular melanomas with an incidence of 0.2–0.8 per million in white population [2, 7]. It is the second most prevalent malignancy of the conjunctiva, after squamous cell carcinoma [8].

CM is typically considered a disease of people with northern European ancestry, occurring most frequently in the Nordic countries (0.9 per milion people CM incidences per year in Norway, 0.8 per milion people per yea in Sweden) [9]. The age-adjusted incidence of conjunctival melanoma per million is 0.49 in non-Hispanic whites, 0.33 in Hispanics, 0.18 in blacks, 0.17 in American Indians, and 0.15 in Asian [1].

5-year survival rate is 83–84% and 5-year recurrence rate is 39% in adult population [2].

It is extremely rare in individuals under 20 years old. Only1% of conjunctival melanoma occurs in children and only 0.68 % of cases develop in patients younger than 14 [1, 2].

CM, like skin melanoma, had slowly increased its incidence during the past decades. Possibly due to aging of population and in ultraviolet (UV) light exposure, which is a known mutagenic factor for sunlight-exposed conjunctiva. However, more recent epidemiological data do not suggest a continuing rising trend in CM incidence [3].

The incidence can be considered equal between men and women, although some studies report a slightly higher incidence amongst males [10].

Pathophysiology

Conjunctival melanoma is composed of variably pigmented malignant melanocytes within the conjunctival stroma [6].

On histopathology, there are atypical melanocytes invading the basement membrane into the substantia propria. In histopathological examination, four different cell types have been described: spindle cells, balloon cells, small polyhedral cells, and large epithelioid cells. It is reported that the epithelioid cell type is correlated with higher morbidity [11].

Precursor lesions

Conjunctival melanoma can arise de novo, from primary acquired melanosis (PAM), or from a conjunctival naevus [4, 12]. Most cases are believed to develop from PAM (42-74%) [4, 9, 13].

Conjunctival naevi are common, but only a small proportion of them (about 2%) undergo malignant transformation. They are ultimately considered the precursor in about 7% of CM cases [4, 9].

In about 11–26% of CM cases, no precursor lesion can be identified [9].

However, the results of a study by B. Masoomian et al. 2023 [14] indicate that in the population of children under 12 years old, up to 90% of conjunctival melanomas did not have a precursor lesion. In the adult population, this percentage was 11-26%.

The most important differences between the three subtypes concern metastasis and mortality. [4].

Ultraviolet radiation

Ultraviolet (UV) radiation is one of the significant risk factors for the development of cutaneous melanoma. However, its impact on the development of conjunctival melanoma remains controversial [2]. CM may arise in both sun-exposed and non-sun-exposed parts of the conjunctiva [11]. UV radiation may be a risk factor for the development of CM, but it is not a necessary factor [9].

Initial identification of the influence of UV radiation on the development of CM was limited due to the limited research capabilities in detecting UV-induced DNA damage. At the time, no potential UV-induced changes in the NRAS gene were observed. Later studies (from 2010-2020) confirmed the presence of mutations typical of UV-induced DNA damage (C → T, CC → TT) in CM samples. These changes mainly affected the TERT promoter [9]. A higher

frequency of mutations was observed in the bulbar conjunctiva, which is more exposed to UV rays. However, contrasting studies have questioned the influence of UV, showing no differences in gene expression between parts of the conjunctiva exposed and not exposed to UV radiation [9].

There is a need for further research on the role of UV radiation, not only in the development, but also in the diagnosis, prognosis, and treatment of conjunctival melanoma, particularly with the use of immunotherapy [9].

Mutations

Known mutations involved in the pathogenesis of conjunctival melanoma include mutations in the BRAF, NRAS, and NF1 genes, as well as rarer mutations in the KIT and PNET genes. These dysfunctions lead to the disruption of the MAPK and PI3K/AKT/mTOR pathways. The PI3K/AKT/mTOR signaling pathway regulates several cellular functions, such as proliferation, metabolism, angiogenesis and metastatic spread [15].

Additionally, abnormalities in telomere function and chromatin remodeling, as well as epigenetic regulation, are significant in the development of CM. They are potentially caused by mutations in the TERT and ATRX genes [3].

Understanding the genetic background of CM may become useful in determining prognosis and could contribute to improving treatment outcomes by facilitating the development of targeted therapies, like the use of vemurafenib in treating cutaneous melanoma [3, 9].

Systematic condition

Higher incidence of the disease is seen in several systemic conditions, including familial atypical mole and melanoma syndrome, xeroderma pigmentosum and neurofibromatosis [16].

Clinical presentation

Conjunctival melanoma shows considerable clinical variability [6]. It is usually presents as an asymptomatic raised pigmented plaque, macule or tumor [2]. The color can range from light to dark brown and only in rare cases these tumors are amelanotic [2]. The lesion can be well circumscribed or diffused. The second one is more frequently seen in cases arising from PAM [16]. Often prominent feeder vessels and surrounding flat PAM are present [6]. It may extend towards the eyelid margin or be contiguous with an eyelid margin melanoma, the globe or the orbit. It may also spread to the tear drainage system or the nose. In this case, it may cause

nosebleeds or tearing, which could be a symptom of the recurrence of nasolacrimal duct melanoma after primary surgical resection [16].

Diagnosis

Any newly developed pigmented lesion on the surface of the eye is suspected to be conjunctival melanoma. In such cases, a thorough ophthalmic examination should be performed, assessing the anterior segment of the eye (slit lamp examination), fundus, and any intraocular infiltrations using invasive methods (gonioscopy) or non-invasive methods such as ultrasound biomicroscopy (UB), in vivo confocal microscopy (IVCM), and anterior segment optical coherence tomography (AS-OCT) [2]. Lymph nodes, especially in the neck region, should be carefully evaluated. If metastasis is suspected, additional imaging studies such as computed tomography, magnetic resonance imaging, or ultrasonography should be performed [2].

Confirmation of the diagnosis can be obtained through histopathological examination of a biopsy, although conjunctival melanoma is not always easy to diagnose. Immunohistochemical studies detecting Melan-A, S-100, and HMB-45 can help achieve a more accurate diagnosis [2].

Diffuse pattern of HMB45 expression in conjunction with a high Ki-67 proliferative index help distinguish melanoma from nevi [17].

Prognosis and outcomes

Research on predictive measures and outcomes in conjunctival melanoma is limited due to the rarity of the disease [16]. Existing data indicate that the 5-year survival rate is 83–84%, and the 5-year recurrence rate is 39% in the adult population [2].

Other data suggest that about 50% of patients experience local recurrence within 10 years, with significant risk factors including the location of the primary lesion on the eyelid and its excision without adjuvant therapy [16].

A predisposition to metastasis includes the primary location of the melanoma in the fornix or tarsal regions, as well as the presence of tumor cells in the surgical margins after excision. Metastatic disease is detected in 26% of patients in a 10-year follow-up and in 32% of patients in a 15-year follow-up [4].

Differences in the risk of metastasis and death also depend on the tumor's origin. One study observed that de novo melanoma is associated with a higher risk of metastasis than melanoma

originating from PAM [4, 5]. Additionally, de novo melanoma shows a higher risk of death after 10 years compared to that originating from PAM [4].

The mortality rate from melanoma after 8 years of follow-up was 13%, with the most important predictive factors identified as de novo origin, fornix location, and nodular configuration [4]. Another strong prognostic factor is tumor thickness: thin lesions of 0.75 mm or less have a survival rate of 100%, while thicker lesions of 3 mm or more have only a 22% survival rate [18].

An unfavorable prognostic factor, increasing the risk of metastasis, local recurrence, and death, also appears to be minimal tumor pigmentation [5].

The prognosis also depends on the location of the lesion. Lesions located in the caruncle, lid margins, palpebral and forniceal conjunctiva, and plica semilunaris have a worse prognosis [2].

Another factor influencing the prognosis is the histological features. Melanomas composed of spindle cells are less aggressive and associated with a more favorable prognosis than mixed cell type lesions [2].

Treatment and Management

Treatment of CM is based on the stage of the disease [19].

The "no-touch" technique is the most used surgical method [20]. It involves excising the lesion with clear margins without touching it. The margin is not precisely defined, ranging from 2 to 5 mm. The procedure is performed under general anesthesia, as local anesthesia can affect tumor architecture and promote local dissemination [21].

The use of adjuvant therapy depends on the practice of the specific center. CM is a rare tumor, so no comparative studies of different adjuvant therapies have been conducted [21]. Additional therapy options include cryotherapy, topical chemotherapy, and adjuvant radiotherapy: brachytherapy or external beam radiotherapy (EBRT) [21].

Cryotherapy is used intraoperatively and involves a double freeze-thaw cycle. A temperature between -70°C and -80°C seems appropriate [18]. Topical chemotherapy should be considered when excised margins are involved with PAM with atypia or residual intraepithelial disease. Mitomycin C at a concentration of 0.04% is most used. Alternatively, interferon alpha 2b can be applied [21].

Radiotherapy is used for invasive CM. Brachytherapy is applied in CM at T1 or T2 stages, utilizing iodine-125, strontium-90, or ruthenium-106 [21]. PBRT is an alternative to brachytherapy, used for small and locally advanced CM in T1, T2, and T3 stages [21].

Orbital exenteration (OE) is a radical and rarely performed surgery. It is typically not a first-line treatment for CM and is reserved for cases with orbital involvement and multiple tumor recurrences [21].

Differential Diagnosis

Conjunctival melanoma should be differentiated from other conditions involving abnormal pigmentation of the conjunctiva, including benign non-neoplastic conditions [5, 6]. These conditions include complexion associated melanosis (CAM), PAM, secondary acquired melanosis, melanocytic hyperplasia, standard melanocytic nevus, blue nevus, extraocular extension of uveal melanoma, scleral thinning [5], as well as gunpowder or mascara deposition, and hemorrhagic cyst following previous surgery [6].

Our research

Search Strategy

To identify the existing literature, a comprehensive search was conducted following the PRISMA guidelines, focusing on presence and characteristic of patients under 18 years suffered conjunctival melanoma. In July 2024, a systematic review of relevant studies was carried out across two electronic databases: PubMed (139 results), Scopus (141 results) and supplemented by an additional 3 results from other sources via manual reference searches. A total of 283 articles were initially identified.

The search strategy utilized the following keywords: (conjunctival melanoma) and (child). There were some limitations during databases research: language was limited to English and study group was selected as “child” (Scopus) or “birth – 18 years” (PubMed). No other limitations were used.

Following screening and eligibility assessment, 20 were deemed relevant and included in the systematic review for further analysis.

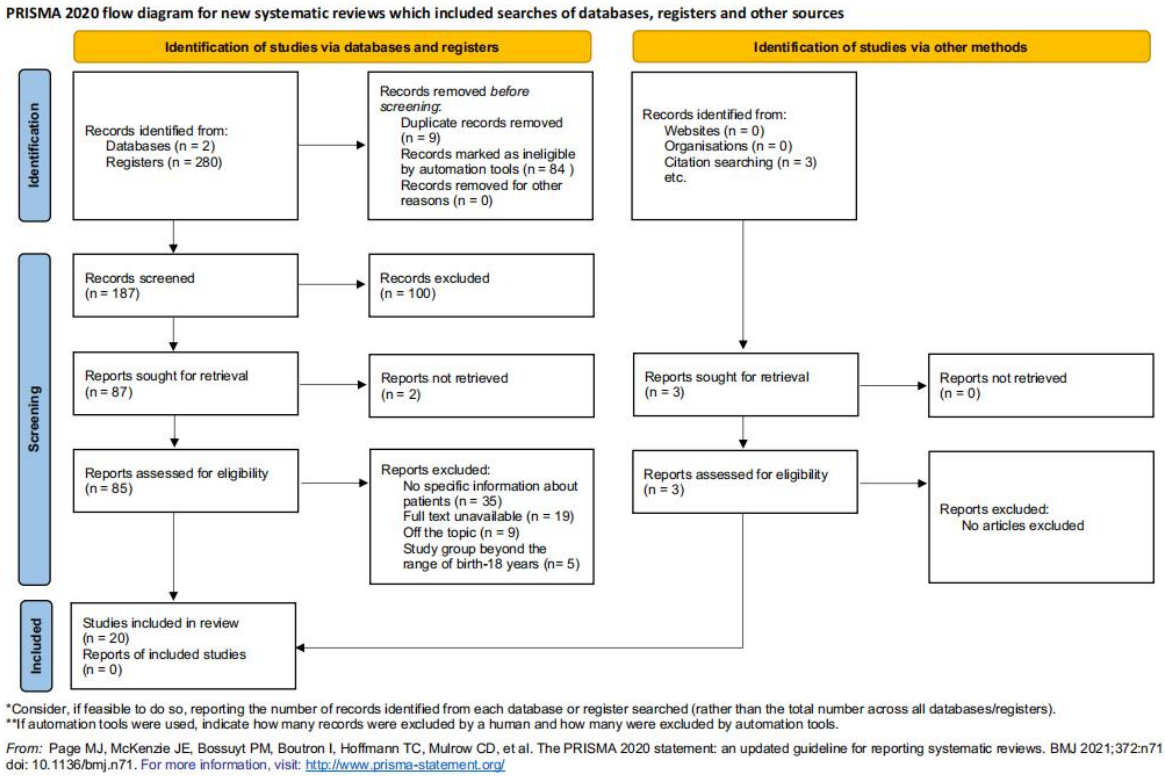
Data extraction and quality assessment

Study selection and data extraction.

All clinical studies about conjunctival melanoma in childhood included detailed information about patient were reviewed and carefully read to evaluate their relevancy.

In the first phase, after delated duplicates, 190 titles and abstracts were analyzed by authors to find suitable articles. In the second phase the full text of 90 selected articles were carefully read. The inclusion criteria were full text available in English, patient/patients age over 18

years old, detailed information about conjunctival melanoma course and patient data. We excluded studies with no separated information about adults and children. No one type of study was preferred at first, but only case studies and case series have been included. Finally, 20 studies described 23 conjunctival melanoma courses in childrenhave been included in the review (detailed information about selection process included in the Figure 1).



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources
Figure 1. – PRISMA 2020 flow diagram

Assessment of the quality of studies

To assess the quality of the included studies we used JBI Critical Appraisal Checklist for Case Reports (results in the Figure 2).

Figure 2. - JBI Critical Appraisal Checklist for Case Reports

	Ciuntu et al. 2018 [18]	Vishnevskia-Dai Et al. 2023 [22]	Bogdănici et al. 2021 [23]	Polat et al. 2008 [24]	Al Masaoudi et al. 2013 [25]	Maria Moral R et al. 2022 [26]	Cantu-Soriano et al. 2024 [27]	Liu et al 2017 [28]	Herwig-Carl et al.2019 [29]	Walters et al. 2017 [30]	Burgués-Ceballos et al. 2013 [31]	Yangzes et al. 2018 [32]	Vasanthapuram et al. 2020 [33]	Saurabah Sharama et al. 2011 [34]	Brownstein et al. 2006 [35]	Akor et al. 2004 [36]	Aoyagi et al 1993 [37]	Stempel et al. 1999 [38]	McDonnell et al. 1989 [39]	Ohguro et al. 2003 [40]
Where patient's demographic characteristics clearly described?	Yes	No	No	Not clear	No	No	No	Not clear	Yes	Not clear	No	Not clear	Not clear	Not clear	Not clear	No	Not clear	No	Not clear	Not clear
Was the patient's history clearly described and presented as a timeline?	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not clear	Yes
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Was diagnostic test or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Not clear	Not clear	Yes	Yes	Not clear	Yes
Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	Not clear	Not clear
Was the post-intervention clinical condition clearly described?	Not clear	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Not clear	Yes	Not clear
Was adverse events (harms) or unanticipated events identified or described?	Yes	Not applicable	Not applicable	Not applicable	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes

Figure 2. – Quality assessment

Results

Study group characteristics

In our research, we collected 23 cases of conjunctival melanoma in children. There were 6 female (26%) and 17 male (74%).

The age of the patients analyzed refers to the time when the study was conducted, which was described in the case report and concerned the lesion identified as conjunctival melanoma in the histological examination. If other lesions had previously occurred in the same location but were excised and histologically not identified as melanoma, they were recorded in the patient's history, but that age was not considered in this analysis.

The age of the patients at the time of the examination, which was part of case study, ranged from 4 to 16 years (median age 10 years). Due to the small amount of data, it was not possible to calculate the age at the time of histological diagnosis.

The age at which melanoma was first observed ranged from birth to 15 years. The total observation time of the lesion until the study ranged from 4 months to 16 years, with an average of 8.44 years. The time between the first examination and the excision of the lesion ranged from the same day to 3 years.

The most often ethnicity was unknown (13 cases – 56.5%), 4 children were White (17.4%), 2 Caucasian (8.7%), 4 Indian Asian (17.4%), 1 Mexican (4.35%), 1 Turkish (4.35%), and 1 mixed White and African American (4.35%).

Personal and Family History

For 12 patients, the case descriptions did not include information on other diseases or moles of the same or different location occurring in the past.

In 4 patients (17.4%), Xeroderma Pigmentosum was diagnosed in childhood. 3 of these were boys. In 1 patient, XP was also diagnosed in a sister.

In 2 patients, other conjunctival nevus had been observed in the past and were excised (one of these cases involved diagnosed XP). In 1 patient, other signs were observed during the study, located on the right shoulder and in the right axilla.

There was no evidence of a family history of malignant melanoma in presented cases.

Detailed information about tumor

The tumor was more frequently located in the right eye (12 cases) than in the left eye (9 cases). Its location on the conjunctiva most often involved the temporal side (10 cases), less frequently the nasal side (4 cases). Most commonly the bulbar conjunctiva (9 cases) was affected. Less commonly the limbus (4 cases), caruncle (1 case), and inferior palpebral conjunctiva with lower eyelid extending to the inferior fornix (1 case).

The pigmentation of the lesion was mostly dark brown in most cases (10 cases), in 3 cases was light, and in 1 case was patchy. Additionally, 3 nevi were reddish (reddish-orange to reddish-brown).

The borders of the lesion were usually irregular (8 cases). In 2 cases the lesion was oval with well-defined borders. 1 lesion was described as elevated, one as flat, and one consisted of 3 lobes. Feeder vessels were observed in 8 cases, while the presence of cysts was noted in 5 cases. In 2 cases, the presence of cysts was denied, and the rest of the data was unavailable.

The size of the lesions varied, with the two largest measuring 20x12 mm and 16x12x7 mm. The thickness of the lesions ranged from 0.2 to 4 mm.

In most cases (19) an increase in size of the lesion was observed, and in 2 cases, this growth was described as rapid. The time during which the increase in the size of the lesion was observed ranged from one month to 4 years from the conducted examination. The time between the initial observation of the lesion and the increase in its dimensions ranged from 0

days (progressive growth from the onset of the lesion) to 14 years after its detection, with an average of 7.3 years.

In the case of 3 lesions, an increase in pigmentation to a more intense color was also observed. Irritative symptoms were present in 1 patient.

Diagnostic and treatment process

In the diagnostic process, examinations such as ophthalmic examination (OE), visual acuity (VA), fundoscopy (FE), intraocular pressure (IP) , ocular motility examination (OM), anterior segment (AS) examination with a slit lamp (SL), B-mode ultrasound (USG-B), lymph node examination (LN), cranial and orbital magnetic resonance imaging (MRI), orbital and brain computed tomography (CT), abdominal ultrasound, EDI-OCT, AC-OCT, AS-OCT, neurological examination, whole body computed tomography, and Gal (Ga) scintigraphy were performed (not every examination was conducted in every case; details are in Figure 3). Most of the examinations did not reveal abnormalities, except for the detection of conjunctival melanoma and its vessels. The only examination that sometimes showed abnormal results was visual acuity (VA), which was 20/40 in 1 case (improving over time after the removal of the lesion) and 1.2 in another case.

All lesions were excised and sent for histopathological and immunohistochemical analysis. Among all the lesions, only one was identified as conjunctival melanoma arising de novo, while the others developed on a preexisting nevus. Histopathological examination results showed that 9 lesions were epithelioid variant, 5 were mixed variant, and 2 were spindle variant. The examined tumors were HMB-45 positive (11/23), S100 positive (6/23), Ki67 positive (5/23), and Melan A positive (3/23) (detailed findings in Figure 3). In 1 case, immunohistochemical testing was not performed, and in 2 other cases, it did not contribute to determining the degree of malignancy.

In addition to excision, cryotherapy was used in 9 cases, alcohol keratoepitheliectomy in 2 cases (details regarding procedures in Figure 3). Additionally, mitomycin C was used in 3 cases: 2 before surgery and 1 after surgery. In 1 case, corticosteroids and postoperative antibiotics were also used, and in another case lubricating eye drops were administered.

The margin size applied during excision ranged from at least 1 to 5 mm. In 6 cases, margins were affected, and reoperation was decided upon. After re-excision margins were free. Recurrence was observed in 2 of these cases and metastasis was observed in 1 of these cases (details in Figure 3).

Outcomes and follow-up

1 patient was lost to follow-up. For another patient, the exact duration of follow-up was unknown. Otherwise, follow-up was conducted for 17 patients, ranging from 1 month to 12 years, with an average duration of 35 months. During this time, 2 patient developed metastasis, 2 patients experienced a recurrence of the lesion on the conjunctiva. 15 patients had no recurrence or metastasis. In 1 case metastasis and recurrence concerned the same patient.

In the first case of metastasis, it was detected 1 month after the removal of the CM. During the clinical examination, a non-tender, firm, 1 cm swelling of the parotid gland was observed, with no enlargement of the cervical lymph nodes. An MRI of the parotid gland showed a parotid lymph node with a necrotic center, suggestive of metastasis, which was confirmed by fine needle aspiration biopsy of the lymph node. Additionally, bone scintigraphy and a CT scan of the chest, abdomen, and pelvis revealed no abnormalities. A left total parotidectomy with facial nerve preservation, ipsilateral neck dissection of levels I, II, and III lymph nodes, submandibular gland excision, and one dose of brachytherapy was performed. Given the stage III melanoma with a high risk of relapse, the patient was started on an induction dose of interferon-α2b along with left neck radiotherapy and topical mitomycin C.

Close monitoring every three months was recommended. During a 12-month follow-up period, no abnormalities were observed.

In the second case, after 5 months of observation, an enlarged ipsilateral parotid node was observed. Metastatic changes were confirmed through diagnostic tests. Systemic chemotherapy was administered for 8 months using cyclophosphamide and dacarbazine. After 15 months of follow-up (20 months from the initial biopsy), no abnormalities were detected.

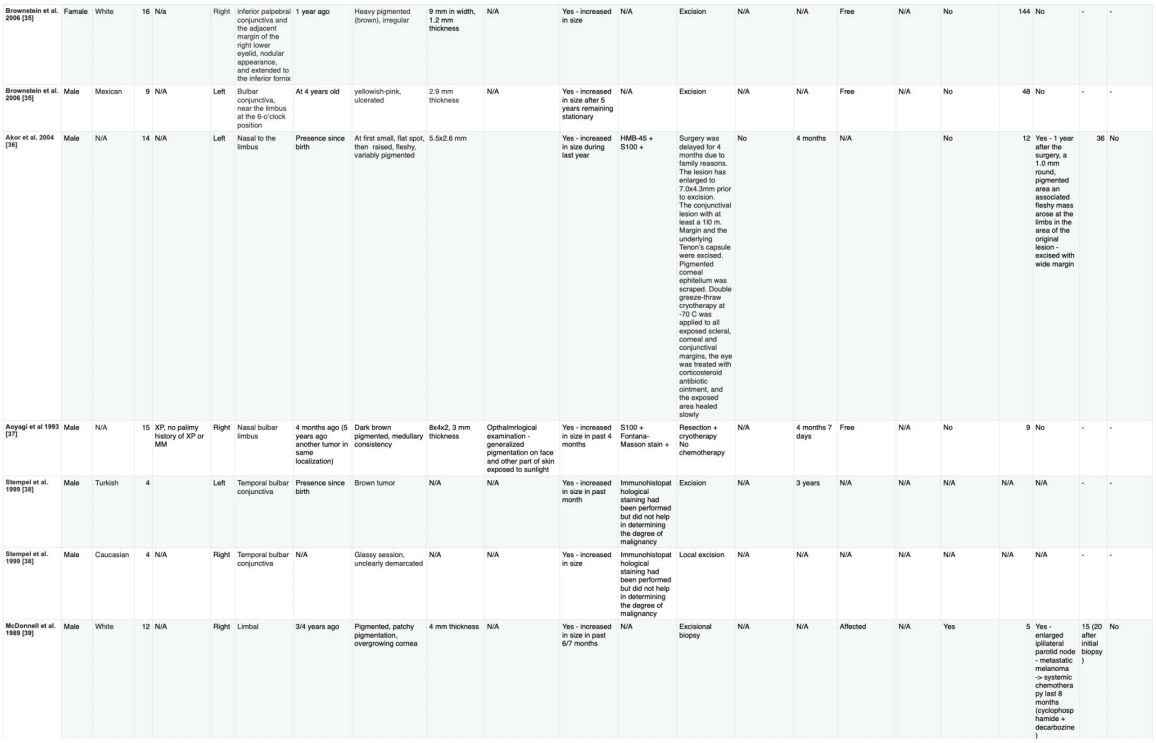
So, summarizing 2 cases of metastasis in parotid lymph node was observed with no other involvement of other organs.

The exact time of the appearance of the lesion was noted in only 1 case, where it occurred over 12 months. In this case, a 1.0 mm round, pigmented area was observed, with an associated fleshy mass arising at the limbus around the original lesion, which was excised with a wide margin. During the subsequent follow-up, which lasted 36 months, there was no recurrence or metastasis observed.

In the second case, the lesion was a fleshy caruncular mass measuring 6 mm at the base and 6 mm in thickness, accompanied by pigmentation of the conjunctival limbus from the 7:00 to 8:00 o'clock position, measuring 5 mm in diameter. The lesion was excised and examined histopathologically, revealing exuberant granulation tissue with no evidence of melanoma. The conjunctival pigmentation was identified as mild benign intraepithelial melanocytic

hyperplasia of the limbal epithelium. The subsequent course of the patient's condition was not reported in the article.

Article	Sex	Ethnicity	Age	Predisposition	Eye	Localization	Apperience	Macroscopic features	Size	Examination	Change in color/ size	Immunochistoche mic findings	Treatment	Application pre/ during/post operation	Time between first examination and resection of tumor	Recested margins	Size of margins	Re-resection needed	Follow up time (months)	Recurrence/ metastasis/ other systemic diseases	Second follow up	Reccurence or secondary systemic disease
Ciuntu et al. 2018 [18]	Male	White	7	N/A	Right	Temporal bulbar conjunctiva	Uncartein - the history is confusing, with possibility of a pre-existing minor, non-penetrating ocular trauma ,the lesion was presented 1,5 years before	non-tender, solitary, sharply demarcated, slightly prominent pigmented mass, oval in shape, with irregular borders and multi-microcystic spaces within the substance, giving rise to a multi-microgranulary formation, which moved freely over the globe, located 3 mm from the corneal limbus, accompanied by dilated episcleral feeding vessels	5.3x3 mm	FE - normal VA - normal AS - normal USG-B - normal LN - absence	Yes - the size and amount of pigmentation increased.	HMB-45 +	Surgical removal with removal of Tenon's capsule, cryotherapy, autologous conjunctival graft for local defect	No	N/A	N/A	At least 1 mm	No	36	No	-	-
Vishnevskia-Dai Et al. 2023 [22]	Male	N/A	7	N/A	Right	Nasal bulbar conjunctiva	Not existed 1 year ago	Reddish lesion, three lobules on the surface of the lesion and a feeder vessel with no cysts	8 mm and thickness of 2.5 mm	FA* - 20/20 FE *- normal LN* - absence AC-OCT - no sclera involvement	Yes - increasing size during previous 3 months	HMB-45 + Ki67+++	„No touch technique" - excisioanal biopsy, cryotherapy under general anesthesia	No	The following day	N/A	4 mm	Yes - wide excision + cryotherapy	73	No	-	-
Bogdănici et al. 2021 [23]	Male	N/A	7	N/A	Right	Temporal conjunctiva	N/A	Heavy pigmented (brown), elevated, irregular	N/A	VA, - normal OP - normal OM - normal SL - normal FE - normal	N/A	CK +++ HMB-45 +++ S100 +++ Ki67 20`5	Surgical removal with removal of Tenon's capsule, cryotherapy, autologous conjunctival graft for local defect	No	N/A	Compound nevus at the edge of excision	At least 1 mm	No	N/A	No	-	-
Polat et al. 2008 [24]	Famale	N/A	6	Unremarkable	Left	Temporal limbus	3 years ago	Reddish-brown lesion - dirty white to brown, accompanied by vascular conversion in temporal limbus	3x4 mm	Cranial and orbital MR - normal Abdominal USG - normal	Yes - increased in size in past 6 mo	HMB-45 +++ S100 +	Complete excision biopsy	0,2% Mytomicyn C - preoperatively, postoperatively Corticosteroid ointment - postoperatively. Antibiotic ointment - postoperatively	N/A	Affected	5 mm	Planned - parents did not permil	6	No	-	-
Al Masaoudi et al. 2013 [25]	Male	N/A	10	N/A	Left	N/A	N/A (at least 3 years)	N/A	8 mm and thickness of 3.5 mm	N/A	Yes - rapid increased in size	N/A	Surgically excised with cryotherapy to the deep margin	No	N/A	N/A	N/A	No	1	Metastasis	12	No
María Moral R et al. 2022 [26]	Male	N/A	10	No	Right	Temporal bulbar conjunctiva	N/A	Reddish-orange lesion, rised, slightly pigmented		Normal (no details)	No at first - rapidly increased in size after 1 year follow up	- Cyclin D1- present In >50% of tumor cells - Diffuse loss of nuclear p16, predominant in the melanocytes population, - positive results for CCND1 and RREB1 (65%, 33%)	Complete excision biopsy with safety margins	0.02% Mytomicyc C postoperatively. Corticosteroid ointment postoperatively Antibiotic ointment postoperatively 2 weeks, 3 times daily	1 year	Affected	N/A	Yes - wide excision of the temporal conjunctiva and Tenon's capsule + cryotherapy + intraoperative 0.02% MMC for 30s defect was treated by grafting of the amniotic membrane	108	No	-	-
Cantu-Soriano et al. 2024 [27]	Famale	N/A	5	Unremarkable	Right	Temporal bulbar conjunctiva	Presence since birth	Heavy pigmented, oval, elevated, well demarcated	0.7 × 0.6 × 0.2 cm (thickness)	VA 20/40 ultrasound biomicroscopy - 1.59 mm vertical x 6.38 mm wide medium reflective lesion on the corneal limbus, between the X and XI meridians, no deep invasion to the sclerae, ciliary body, or adjacent structure	Yes - increasing size during previous 2 years	HMB-45 + Ki67 20%	Wide-excisional biopsy, lamellar sclerectomy, perilimbal lamellar keratectomy, and cauterization of feeder vessels were performed, followed by an autologus conjunctival graft from the ipsilateral (right) eye measuring 12 × 5 mm	lubricating eye drops - daily, postoperatively	nd.	Clear	2 mm	No	2	No	-	-
Liu et al 2017 [28]	Famale	White	9	N/A	Left	Bulbar conjuntiva	At 4 years	Small, darkly pigmented, flat		VA - 20/20 SL - 4 x 3 mm darkly pigmented, raised lesion at the temporal limbus, with fine surrounding vessels, examination was negative for feeder vessels or additional pigment of the bulbar or palpebral conjunctiva of both eyes. Dilated fundus examination - unremarkable EDI-OCT - elevated, hyperreflective lesion over the sclera without deep invasion and with shadowing	Yes - increased in size in past 4 years	HMB-45 +++ Ki67 +	„No touch technique" - excisioanal biopsy, Tenon's capsule resection, cryotherapy.	No		Affected	N/A	corneal epitheliectomy, cryotherapy, and an amniotic membrane graft	30	No	-	-
Herwig-Carl et al.2019 [29]	Famale	Caucasian	14	Unremarkable	Right	Nasal bulbar conjunctiva	2/3 years ago	Brown - heavy pigmented	2 × 1 × 1 mm	N/A	Yes - slow increased size over several months	HMB-45 + S100 + Ki67 -	Excisional biopsy	No	The same day	Clear	N/A	No	Lost to follow up	-	-	-
Walters et al. 2017 [30]	Male	Mixed white and African American	10	N/A	left	Left caruncle	Presence since birth	flesh-colored lesion	2.5 mm thickness	VA - 20/20 omprehensive ophthalmic examination - normal	Yes - increased in size in past 3 months	Ki67 >5%	Excision	No	2 weeks	Affected	N/A	„No touch technique" with cryotherapy + reconstruction with amniotic membrane	Yes - no detailed time (at Willis Eye Hospital)	fleshy caruncular mass 6 mm at the base and 6 mm in thickness and pigmentation of the conjunctival limbus from the 7:00 to 8:00 o'clock position measuring 5 mm in diameter.	No	-
Burgués-Caballos et al. 2013 [31]	Male	N/A	15	N/A	Left	Adjacent to the limbus, temporal	Presence since childhood	pigmented, elevated mass, reaching the limbus, with marked vascularization at first ocular examination, two months later, it presented evident growth with conjunctival ulceration.	11 × 9-mm		Yes - the size and amount of pigmentation increased previous last 2 years	HMB-45 + S100 + Melan a +	After first examination parents rejected biopsy, after 2 months wide microsurgical excisional biopsy was performed - "no-touch" technique	No	2 months	Clear	3 mm	No	10	No	-	-
Yangzes et al. 2018 [32]	Male	Asian Indian	16	N/A	Right	Temporal bulbar conjunctiva, extending from the limbus up to the lateral canthus	Presence since childhood	a large brownish lesion, involved almost entire temporal aspect of the bulbar conjunctiva, initially pin-head sized	20 × 12 mm	AS-OCT - cystic spaces and sclera appeared to be spared	Yes - increased in size in past 2 years	HMB-45 + Ki67 + Melan A +	„No touch technique" - excisioanal biopsy + cryotherapy	0.04% MMC - one weekly on and off cycles		N/A	4 mm	No	9	No	-	-
Vasanthapuram et al. 2020 [33]	Male	Asian Indian	9	XP	N/A	Bulbar conjunctiva, corneal involvement	N/A	Pigmented, corneal involvement	N/A	N/A	N/A	N/A	Wide excision biopsy + alcohol karatoepitheliectomy + cryotherapy + AMG	N/A	N/A	N/A	N/A	No	101	No	-	-
Vasanthapuram et al. 2020 [33]	Famale	Asian Indian	12	XP	N/A	Bulbar conjunctiva, corneal involvement	N/A	Pigmented	N/A	N/A	N/A	N/A	Wide excision biopsy + alcohol karatoepitheliectomy + cryotherapy + AMG	N/A		N/A	N/A	No	11	No	-	-
Saurabah Sharama et al. 2011 [34]	Male	Asian Indian	14	XP, sister XP, no other cases of XP or MM in family	Left	Bulbar conjunctiva, corneal involvement	Since 6 months of age	Hyperpigmented swelling	16x12x7 mm	FE - normal rutine haematological investigation - normal orbital and brain CT - normal neurological examination - normal lymphadenopathy - absence	N/A	Did not done	Wide and lid econstruction under bulbar anesthesia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-	-



Brownstein et al. 2006 [35]	Famale	White	16	N/a	Right	inferior palpebral conjunctiva and the adjacent margin of the right lower eyelid, nodular appearance, and extended to the inferior fornix	1 year ago	Heavy pigmented (brown), irregular	9 mm in width, 1.2 mm thickness	N/A	Yes - increased in size	N/A	Excision	N/A	N/A	Free	N/A	No	144	No	-	-
Brownstein et al. 2006 [35]	Male	Mexican	9	N/A	Left	Bulbar conjunctiva, near the limbus at the 6-o'clock position	At 4 years old	yellowish-pink, ulcerated	2.9 mm thickness	N/A	Yes - increased in size after 5 years remaining stationary	N/A	Excision	N/A	N/A	Free	N/A	No	48	No	-	-
Akor et al. 2004 [36]	Male	N/A	14	N/A	Left	Nasal to the limbus	Presence since birth	At first small, flat spot, then raised, fleshy, variably pigmented	5.5x2.6 mm		Yes - increased in size during last year	HMB-45 + S100 +	Surgery was delayed for 4 months due to family reasons. The lesion has enlarged to 7.0x4.3mm prior to excision. The conjunctival lesion with at least a 1t0 m. Margin and the underlying Tenon's capsule were excised. Pigmented corneal ephitelium was scraped. Double greeze-thraw cryotherapy at -70 C was applied to all exposed scleral, corneal and conjunctival margins, the eye was treated with corticosteroid antibiotic ointment, and the exposed area healed slowly	No	4 months	N/A		No	12	Yes - 1 year after the surgery, a 1.0 mm round, pigmented area an associated fleshy mass arose at the limbs in the area of the original lesion - excised with wide margin	36	No
Aoyagi et al 1993 [37]	Male	N/A	15	XP, no palmy history of XP or MM	Right	Nasal bulbar limbus	4 months ago (5 years ago another tumor in same localization)	Dark brown pigmented, medullary consistency	8x4x2, 3 mm thickness	Opthalmrlogical examination - generalized pigmentation on face and other part of skin exposed to sunlight	Yes - increased in size in past 4 months	S100 + Fontana-Masson stain +	Resection + cryotherapy No chemotherapy	N/A	4 months 7 days	Free	N/A	No	9	No	-	-
Stempel et al. 1999 [38]	Male	Turkish	4		Left	Temporal bulbar conjunctiva	Presence since birth	Brown tumor	N/A	N/A	Yes - increased in size in past month	Immunohistopathological staining had been performed but did not help in determining the degree of malignancy	Excision	N/A	3 years	N/A	N/A	N/A	N/A	N/A	-	-
Stempel et al. 1999 [38]	Male	Caucasian	4	N/A	Right	Temporal bulbar conjunctiva	N/A	Glassy session, unclearly demarcated	N/A	N/A	Yes - increased in size	Immunohistopathological staining had been performed but did not help in determining the degree of malignancy	Local excision	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-	-
McDonnell et al. 1989 [39]	Male	White	12	N/A	Right	Limbal	3/4 years ago	Pigmented, patchy pigmentation, overgrowing cornea	4 mm thickness	N/A	Yes - increased in size in past 6/7 months	N/A	Excisional biopsy	N/A	N/A	Affected	N/A	Yes	5	Yes - enlarged ipilateral parotid node - metastatic melanoma -> systemic chemotherapy last 8 months (cyclophosphamide + decarbozine)	15 (20 after initial biopsy)	No
Ohguro et al. 2003 [40]	Male	N/A	14	No	Right	Temporal bulbar conjunctiva	2 years ago	Pigmented, round, clear margin	4 mm in diameter, 0.5-0.8 mm in height	VA - 1.2 IP - 18 mmHg OE - no abnormalities in left eye SL - pigmented tumor not attached to the limbus FE - no abnormalities Whole body CT - no abnormalities Ga scintigraphy - no abnormalities	Yes - increased in size	HMB-45 + Melan A +	Resection	No		Affected	2 mm	Yes - wider resection + cryopexy	N/A	No	-	-

Figure 3. - Summary of the information collected [18, 22-40].

Discussion

Our review presents 23 cases of conjunctival melanoma that occurred before the age of 18. 17 of 23 (74%) of these cases were boys, which might suggest a certain gender predisposition. A similar observation was made in the study by B. Masoomian et al. 2023 [14]. However, in the study by Shields et al. 2017 [8], opposite results were obtained, with a higher incidence of CM observed among girls (67% vs. 33%). In the adult population, the gender distribution in the available studies also varies [41-45]. Caution should be exercised when comparing differences in populations of different ages. However, this indicates the need for further research to analyze the distribution of cases among both sexes in the population under 18 years of age.

In most patients (12/18), no potential risk factors for melanoma development, including family history, were identified. However, many genetic mutations are involved in the

pathogenesis of conjunctival melanoma so it could be not discovered [46]. Due to the limited amount of data, the analysis of possible risk factors is significantly constrained.

In our review, the time of first observation of conjunctival melanoma and the time of diagnosis varied greatly, ranging from birth to 15 years of age and from 4 to 16 years of age, respectively. This shows that the development of melanoma can occur at any age. So, any new retinal lesion should be thoroughly diagnosed. However, in the Shields et al. 2017 [9] study, a significant increase (peak) in cases was observed in the age range of 15-21 years, which may be a time of oncological vigilance.

The mean follow-up time in the study by B. Masoomian et al. 2023 [13] was longer than in ours: 50 months compared to 35 months. A higher recurrence rate after excision (20%) was also observed. In our study, this rate was 11.8%. This indicates the need for long-term follow-up to evaluate outcomes.

In the study by B. Masoomian et al. 2023 [13], a higher incidence of metastases was also observed. These involved 5 patients (19%). The observed metastases were in the parotid gland (n = 2), orbit (n = 1), multiple organs (n = 1), and lymph nodes (n = 1). In our review, metastases occurred in 2 patients (11.8%). Both cases involved the parotid gland. Once again, the reason for the higher observed metastasis rate may be the longer follow-up time. Additionally, this further proves the aggressive nature of conjunctival melanoma and the necessity of thorough and regular examinations to detect potential metastases.

Among patients who experienced local recurrence (2 patients), 50% had affected margins after the first histopathological examination. The same situation occurred in patients who were diagnosed with metastasis. In the case of conjunctival melanoma, the first surgery is the most important and plays a crucial role in preventing recurrence, metastasis, and death. Therefore, it should be performed in experienced centers [9].

The limitations of our study include the small number of included articles and patients, which does not allow for drawing prognostic conclusions for the population. The small number of included studies may be due to the selection process, as not all studies may have been included in the review due to lack of access to the text and the language of publication. Another limitation could be the variability in the description of the selected cases, which contributed to the absence of some data, thereby limiting the possibility of analysis.

Conclusion

Conjunctival melanoma is a rare condition, especially in children and adolescents. Due to its potentially aggressive course and tendency for metastases and recurrences, oncological

vigilance is essential in every case of conjunctival lesions, aiming for early detection and treatment. The amount of data on this topic is limited, so further research on conjunctival melanoma in children is necessary to establish prognosis and age-specific diagnostic and therapeutic strategies. A greater number of studies in the future may also contribute to the development of new treatment options and improved prognosis.

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