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Histological and clinical evaluation of conjunctival pigmented lesions in children and adolescents

Ocena kliniczna i histopatologiczna zmian barwnikowych spojówki u dzieci i młodzieży

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Abstract: Purpose: To analyze histological and clinical features of pigmented conjunctival lesions in children and adolescents.
Material and methods: Series of surgically removed conjunctival lesions were analysed retrospectively at Ludwik Zamenhoff University Paediatric Hospital between 2001 and 2016.
Results: 30 pigmented lesions in 30 children (mean age 11.2 years) were excised during the analyzed period. The anatomical locations of the lesions included bulbar conjunctiva (46.7%), juxtalimbal area (without corneal involvement) (26.7%), lacrimal caruncle (20%), and plica semilunaris (6%). Histopathological diagnosis was: compound nevus (73.4%), junctional nevus (23.3%) and malignant melanoma (3.3%). The postoperative course was uneventful in all cases and there was no recurrence in patient with melanoma.
Conclusions: Although conjunctival nevi in children are usually benign, malignant melanoma should be taken into account during diagnosis and treatment.

Key words: conjunctival nevi, melanoma, children, adolescents.

Abstrakt: Cel: analiza kliniczna i histopatologiczna zmian barwnikowych spojówki u dzieci i młodzieży.
Materiał i metody: retrospektywna analiza usuniętych znamion barwnikowych spojówki w latach 2001–2016.
Wyniki: w analizowanym okresie wycięto 30 barwnikowych zmian u 30 dzieci (średni wiek dzieci 11,2 roku). Zmiany były umiejscowione w: spojówce gałkowej – 46,7%, spojówce przyrąbkowej (bez zajęcia rogówki) – 26,7%, mięsku łzowym – 20%, i fałdzie półksiężycowatym – 6%. W badaniu histopatologicznym rozpoznano: znamię złożone – 73,4%, znamię brzeżne – 23,3%, i czerniaka – 3,3%.
Wnioski: wprawdzie znamiona barwnikowe spojówki u dzieci i młodzieży mają zwykle charakter łagodny, niemniej jednak trzeba pamiętać, że u dzieci z tej grupy wiekowej może wystąpić czerniak.

Słowa kluczowe: znamiona spojówki, czerniak, dzieci, młodzież.
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Introduction

Conjunctival nevi are the most common ocular surface tumors in children (1). If clinically stable, they do not require treatment (2). Excision is recommended in lesions which change in size or color, recur or for cosmetic indications (3, 4). Conjunctival pigmented nevi deserve special attention. The vast majority of nevi are benign and appear to carry no risk for the development of melanoma during childhood (1, 5). Besides, conjunctival melanoma (potentially lethal, even after prompt and proper treatment) typically occur in adults at the mean age of 62 years. Here, we report our experience with young patients with conjunctival pigmented lesions treated over thirteen years.

Material and methods

The study approved by the University Ethic Committee was carried out in a children hospital that serves the North-East Poland population of 1.2 mln inhabitants. We retrospectively reviewed medical records of 30 patients who underwent surgical excision of a pigmented conjunctival lesion between November 2001 and December 2016. In all cases, the final diagnosis was established based on histological evaluation of tissue specimens. All patients were monitored postoperatively with a minimum follow-up of 5 months.

Results

Thirty eyes of 30 patients (19/ 63.3% girls and 11/36.7% boys, mean age of 11.2 years, range of 4.0 – 17.5 years) with pigmented conjunctival nevus were analyzed. The mean follow-up was 3.8 years (range of 5 months – 6 years). All patients had visual acuity of 1.0 and normal intraocular pressure. The nevus was located in the right eye in 16 patients and in the left eye in 14 patients. The clinical features of conjunctival nevi are presented in Table I.

Number of eyes/ Liczba oczu	Histological diagnosis/ Rozpoznanie hist.-pat.	Anatomical location/ Umiejscowienie zmiany
22	compound naevus/ znamię złożone	bulbar conjunctiva (11 eyes)/ spojówka gałkowa (11 oczu) juxtalimbal conjunctiva (5 eyes)/ spojówka przyrąbkowa (5 oczu) lacrimal caruncle (5 eyes)/ mięsko łzowe (5 oczu) plica semilunaris (1 eye)/ fałd półksiężycowaty (1 oko)
7	junctional naevus/ znamię brzeżne	bulbar conjunctiva (3 eyes)/ spojówka gałkowa (3 oczu) juxtalimbal conjunctiva (3 eyes)/ spojówka przyrąbkowa (3 oczu) lacrimal caruncle (1 eye)/ mięsko łzowe (1 oko)
1	melanoma/ czerniak	Plica semilunaris (1 eye)/ fałd półksiężycowaty (1 oko)

Tab. I. Clinical and histopathological features of excised conjunctival nevi.
Tab. I. Cechy kliniczne i histopatologiczne znamion spojówkowych.

The anatomical locations of the studied nevi included bulbar conjunctiva (14 eyes, 46.7%), juxtalimbal area without corneal involvement (8 eyes, 26.7%), lacrimal caruncle (6 eyes, 20%), and plica semilunaris (2 eyes, 6%). The nevus was situated temporally (16 eyes, 53.3%), nasally (13 eyes, 43.3%) and superiorly (1 eye, 3.3%). Parents and carers of all enrolled children reported color or size change after which the lesion became more noticeable, so they were concerned it could be cancer. All nevi were excised under general anaesthesia, using the 'non-touch' technique. Postoperative course was uneventful in all cases. Histopathological diagnosis was: compound nevus in 22 eyes (73.4%), junctional nevus in 7 eyes (23.3%) and malignant melanoma in one eye (3.3%). It was a 13-year-old girl with intellectual disability. She was referred to the ophthalmology clinic with conjunctival nevus in her right eye. Her parents reported that a lesion, which developed two years earlier, became more noticeable following a rapid increase in size over the last few months (Fig. 1).

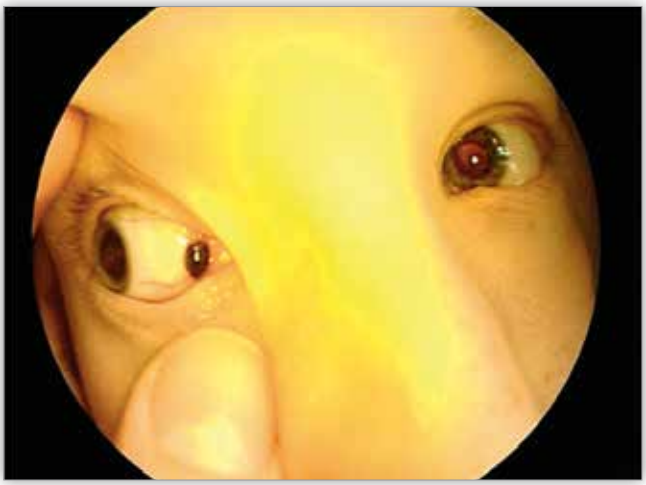

Fig. 1. Melanoma of plica semilunaris in a 13 year-old girl.
Ryc. 1. Czerniak fałdu półksiężycowatego spojówki u 13-letniej dziewczynki.

Clinical diagnosis of a nevus of semilunar conjunctival fold, sized 7.0 mm x 4.0 mm was made and the lesion was surgically excised on January 13, 2009 with 3.0 mm healthy margin of normal-appearing conjunctiva, with adjuvant cryotherapy. Histological evaluation demonstrated melanoma with maximum-base diameter of 7.0 mm and thickness of 2.0 mm (as measured using Breslow method) (Fig. 2).

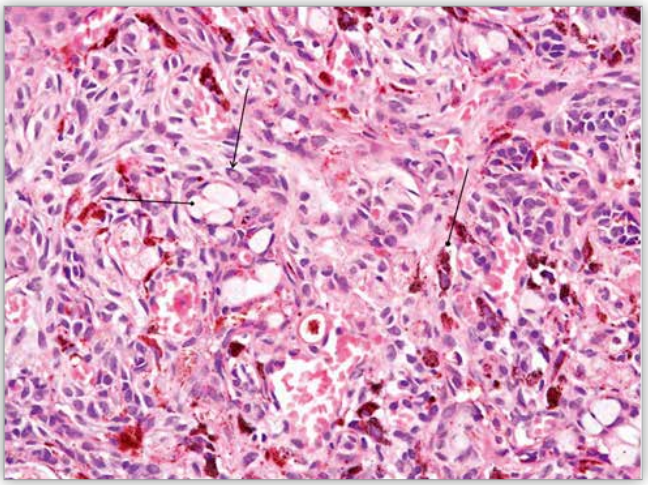

Fig. 2. Intranuclear inclusion typical of melanoma cells, with nuclear atypia. The features of conjunctival gland infiltration and multiple melanin deposits. Magn. 400x.
Ryc. 2. Wewnątrzjądrowe inkluzje typowe dla komórek czerniaka, z jądrową atypią. Cechy infiltracji gruczołów spojówkowych i liczne zlogi melaniny. Powiększenie 400x.

All margins were clear. The patient was treated with α-2b interferon (10 MU/m^2, three times a week, s.c.) as adjuvant therapy between March 9, 2009 and March 5, 2010, which was well tolerated. The patient still remains under regular follow up in the ophthalmology and oncology clinics with no evidence of recurrence or metastasis eight and a half years after melanoma excision (Fig. 3).

Fig. 3. Right eye 6 years following melanoma excision.
Ryc. 3. Oko prawe po 6 latach od operacji usunięciu czerniaka.

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Discussion

Nevi are the most common melanocytic lesions of the conjunctiva, accounting for 52% of all cases (6). Conjunctival nevi are benign, melanocytic, circumscribed, sessile, slightly elevated tumors usually located close to the limbus, with no corneal involvement, with onset within the first two decades of life. Nevi can increase in size and change in colour during puberty or pregnancy. In the pediatric population, conjunctival nevi are more prevalent, representing 64% of 262 pediatric tumors of the conjunctiva (1). They constitute a cosmetic problem and cause significant mental burden, especially when large and noticeable due to their location (4).

Nevi are typically located in the interpalpebral bulbar conjunctiva (67–72%), followed by the lacrimal caruncle (15–22%) and tarsus (0.7%) (5, 6). Tarsal melanocytic lesions are frequently regarded as suspicious for malignancy. In the present study, most cases of conjunctival nevi (58.3%) were localized on the interpalpebral bulbar conjunctiva (Tab. I) and this is the most common location also in other reports (1, 6–8). Six (20%) of our patients had melanocytic lesions of the lacrimal caruncle. Approximately 14% of pediatric conjunctival nevi are seen on the caruncle or plica semilunaris (1). Having examined 191 patients with lesions of the lacrimal caruncle, Kaeser et al. believe that pigmented lesions should be monitored carefully due to poor prognosis of caruncular melanoma (9). They concluded that in the absence of clear criteria for malignancy, any change in color, size, or vascularization of a caruncular lesion should hasten excision. In the present study, juxtalimbal nevi were observed in eight eyes (26.7%) and none of these lesions showed corneal involvement. The nevi were most often temporal (16 eyes, 53.3%), nasal (13 eyes, 43.3%) and superior (one eye, 3.3%). Shields et al also described similar localization of 872 melanocytic tumors (7).

Conjunctival nevi are classified as junctional, compound and subepithelial. In the present study, compound nevi were the most frequent histologically diagnosed type of conjunctival nevus – they were observed in 22 eyes (73.4%) (Tab. I). In the literature, compound nevi are the most common type of conjunctival nevus, accounting for about 70% to 78% of all nevi (2, 8). Pure junctional nevi are rare except in childhood (2,10). In the present study, junctional nevi were observed in 7 eyes (23.3%). This confirms the conclusion by Shields et al. that compound and junctional nevi are usually found in younger aged group, while subepithelial nevi are usually found in older aged group (2). Subepithelial nevi, prevalent in the older age groups, represent about 9 percent of all conjunctival nevi (2, 3). We did not observed this type of nevi in our patients, maybe due to relatively small group of patients and their age (mean age of 11.2 years).

Conjunctival nevi do not require treatment if they are clinically stable (2, 7). Excision is recommended if lesions show any clinical features of possible malignancy, or for cosmetic appearance (3). In the present study, parents/ carers of all enrolled children reported lesion which became more noticeable after color or size change as their chief complaint, and mentioned concern of possible malignant character of the lesion as their important motivation. Other presumable reason to opt for the surgery was aesthetic appearance. Alkatan et al. reported it as the most common indication for conjunctival nevi excision, true for 38% of lesions, whereas in 33% of cases, there no specific indication for surgery (8). We decided to excise conjunctival lesions mostly due to parents concern about melanoma, but cosmetic reasons should also be considered, especially that 63% of our patients were girls.

Conjunctival nevi appear to carry extremely small risk for the development of melanoma during childhood, so histological confirmation of melanoma in a 13-year-old girl came as a surprise. It is estimated that only 1% of all conjunctival melanomas affects children and they are mainly reported in the form of case studies (1, 10, 11). Conjunctival melanomas in children have a variable prognosis, with high metastasis and mortality rates (5). A review by Taban and Traboulsi found only 28 reported cases from 2007 (with only eight cases with sufficient clinical detail) of conjunctival melanoma in children younger than 15 years (12). Conjunctival melanoma may arise from a preexisting nevus (5% of cases), primary acquired melanosis (PAM) (53–75%) or *de novo* without any precursor at all (18–30%) (3, 11, 13). Clinical features suggestive of melanoma include large size, variegated appearance, immobility in relation to the sclera, extension onto the cornea, presence of multiple feeder vessels, and evidence of canalicular obstruction (3, 14). The colour ranges from light to dark brown, rare cases are amelanotic. The most common location of the lesion is bulbar conjunctiva close to the limbus, usually within the temporal quadrant in children (10). Our patient presented with a two-year history of dark brown, asymptomatic nevus of the right plica semilunaris, without any feeder vessels, which had recently increased in size.

The primary treatment for conjunctival melanoma is surgical excision using a minimal touch technique, which should always be combined with adjuvant therapy to minimize local recurrence (13). Adjuvant therapy may consist of intraoperative cryotherapy, radiotherapy, topical chemotherapy and/or immunotherapy (13, 15–18). In our melanoma patient, we chose a 'no-touch' technique of surgical excision followed by application of supplemental cryotherapy to the surgical margins. Fortunately, histological evaluation of excised lesion confirmed free margins.

Various clinical and pathological factors have been attributed to an increased risk of melanoma recurrence, such as excision without adjuvant cryotherapy, presence of tumor at excision margin, tumors thicker than 2.0 mm, and multifocal location (14, 16–18). A literature search made by Masaoudi et al. in 2013 revealed 11 cases of conjunctival melanoma reported in children, with only two cases of metastases (11). Survival may be improved by early diagnosis of regional metastases with preauricular lymph nodes typically being the most common first site of metastases. Retrospectively, most distant metastases seem to occur in liver, lung and brain, so screening should focus on these organs (17). Regular follow-up appointments are obligatory, because even when tumor margins are histologically shown to be clear, recurrence of conjunctival melanoma still remains a significant clinical problem (15).

It was demonstrated that adjuvant therapy may reduce the number of local recurrences (18). Novel adjuvant approaches include e.g. topical interferon α-2b immunotherapy

and topical VEGF inhibitors (18). In order to improve survival after melanoma excision, our patient was treated with subcutaneous α-2b interferon for 48 weeks. She was reassessed every three months for the first five years following surgery, and now, as an adult, every six months, with no evidence of metastases either clinically or in imaging studies, including MRI. She is also monitored three times a year with slit lamp biomicroscopy to detect any local recurrence. Current practice is to follow all conjunctival melanoma patients annually until ten years following surgery (16).

In conclusion, although conjunctival nevi in children are usually benign, malignant melanoma should be taken into account in this age group.

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