https://doi.org/10.5114/oku/199410 (Revievs Papier)
Received: 6.06.2024 Accepted: 22.07.2024

Pigmented Conjunctival Lesions

Magdalena Dębicka-Kumela[1,2], Joanna Kowal[1,2], Agnieszka Nowak[1], Karolina Gerba-Górecka[1], Dagmara Nowak[1], Natalia Mackiewicz[1], Bożena Romanowska-Dixon[1,2]

[1] Department of Ophthalmology and Ocular Oncology, University Hospital in Krakow, Poland
Head: Prof. Bożena Romanowska-Dixon, PhD (hab.), MD
[2] Department of Ophthalmology, Jagiellonian University Medical College, Krakow, Poland
Head: Prof. Bożena Romanowska-Dixon, PhD (hab.), MD

Summary: Pigmented conjunctival lesions include nevi, primary acquired melanosis (both with and without atypia), and the rarest form, conjunctival melanomas. In cases of lesions suspected of malignant transformation, the treatment of choice is radical surgical excision. If melanoma is confirmed, additional local treatments are often employed, including chemotherapy, immunotherapy, or radiation therapy. In the diagnosis of conjunctival melanoma, it is beneficial to use the pattern analysis algorithm.

Key words: conjunctival malignant melanoma (CMM), primary acquired melanosis (PAM), conjunctival pigmented nevus.

Pigmented conjunctival lesions can be either benign or malignant [1, 2]. Malignancies are less frequently diagnosed but pose a significant threat to the patient's life. Any lesion excised from the conjunctiva should undergo histopathological evaluation [3]. Melanocytic conjunctival lesions include nevi, primary acquired melanosis (PAM), and conjunctival malignant melanoma (CMM). In the differential diagnosis of pigmented conjunctival lesions, considerations should include not only those mentioned above but also extraocular invasion of ciliary body melanoma, melanosis associated with systemic diseases, the presence of a foreign body, effects caused by drugs (e.g. epinephrine) or cosmetics (e.g. mascara), and racial melanosis [4].

Nevi are the most common, accounting for 52% of melanocytic lesions and 28% of all conjunctival tumors [5–7]. Nevi are benign, with a transformation risk to melanoma of less than 1% [7, 8]. Initially, nevus cells are located at the junction between the epithelium and the substantia propria (junctional nevi). Over time, these cells migrate deeper into the substantia propria, forming compound nevi, and eventually, they lose contact with the epithelium, resulting in subepithelial nevi. They are most commonly found unilaterally on the bulbar conjunctiva, appearing slightly convex with varying degrees of pigmentation. These lesions may also contain cysts and feeding vessels (Fig. 1) [7, 9]. Each conjunctival nevus requires ophthalmological monitoring, preferably supplemented with photographic documentation. If any changes in the size, shape, or color of a nevus are observed, neoplastic transformation should be suspected, and the treatment should follow the protocol for malignant tumors. Nevi are sometimes surgically removed for cosmetic reasons [8, 10]. Primary acquired melanosis accounts for 11% of all conjunctival lesions and 21% of pigmented conjunctival lesions [6, 11, 12]. It originates from the proliferation of melanocytes within the conjunctival epithelium. In patients with melanosis, identifying atypia through histopathological examination is crucial, as PAM with atypia progresses to melanoma in 12% to 50% of cases, whereas PAM without atypia carries no risk of malignant transformation [2, 4, 8–11, 16]. Unfortunately, these changes are clinically very challenging to differentiate [8, 17]. Primary acquired melanosis typically presents as a unilateral, flat, brown pigmented lesion on the conjunctiva, lacking visible vascularization. It can either be localized to a small area or diffuse (Fig. 2) [18]. PAM with atypia is more likely to exhibit features including black pigmentation, an amorphous pattern, asymmetry in both pattern and color, and the presence of black dots (Fig 3) [9]. Primary acquired melanosis with atypia is regarded as a form of melanoma *in situ*, akin to lentigo maligna [11, 19].

Fig. 1. Conjunctival nevus.

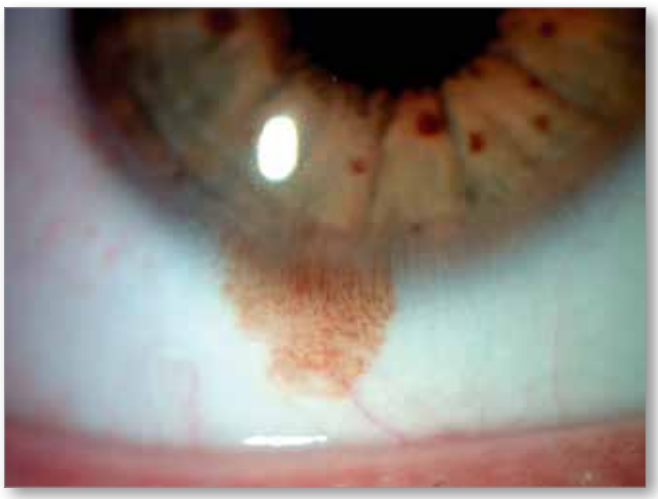

Fig. 2. PAM without atypia.

ISSN 1505-2753

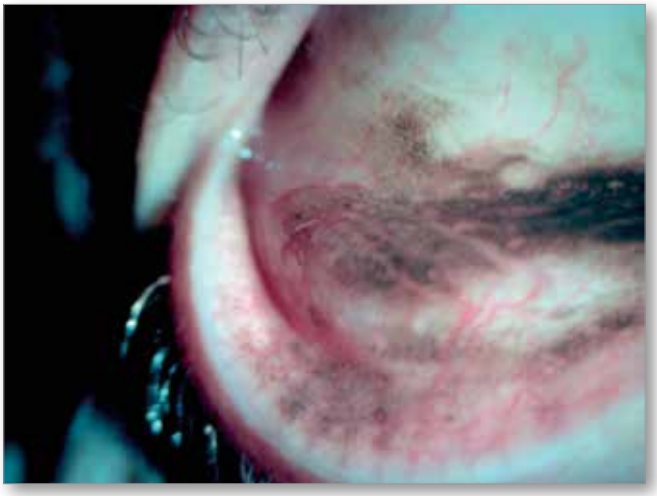

Fig. 3. PAM with atypia.

The treatment of choice for PAM (according to Shields et al.) is either observation or surgical excision, often combined with cryotherapy and/ or local chemotherapy, depending on the size of the lesion. For very large lesions, multifocal biopsy (conjunctival mapping) is recommended [8, 11].

Conjunctival melanoma is a rare tumor, comprising approximately 1–5% of ocular melanomas and only 1.6% of all non-cutaneous melanomas [20, 21]. Over the past decade, the incidence of this cancer has risen, likely due to increased exposure to ultraviolet radiation [8, 21]. In children, CMM is very rare [22, 23]. The development of CMM is attributed to the hyperplasia of melanocytes within the basal layer of the conjunctival epithelium. This tumor most commonly (in 50–75% of cases) develops from primary acquired melanosis with atypia, arises *de novo* in approximately 5–37% of cases, and originates from a pigmented nevus in 4–25% of cases [2, 8, 11, 12, 16, 20–27). Melanomas arising from precursor lesions generally have a more favorable prognosis compared to those developing *de novo*. The mortality rate associated with conjunctival melanoma reaches 30% over a 10-year follow-up period (8, 14, 16, 21, 24, 28). Conjunctival melanoma metastasizes through lymphatic vessels (typically to the preauricular or submandibular lymph nodes) or via the bloodstream (most commonly to the liver, brain, lungs, and skin). It can also spread by continuity, invading the globe or orbit [14, 19, 24, 27, 29]. The presence of lymph node involvement is associated with a better prognosis compared to metastases in distant organs [16]. Metastases are estimated to occur in 32% of cases over a 15-year follow-up period [8, 24]. The risk of local recurrence is very high, ranging from 19–45% at 5 years, 26–59% at 10 years, and 65–70% at 15 years of follow-up [12, 19, 21, 24, 29, 30–32]. Recurrence is most frequently observed between 11 and 17 months after diagnosis [12, 20, 21, 29, 31]. Unfavorable prognostic factors for recurrence and metastasis include tumor location in the retrobulbar conjunctiva, multifocality, tumor thickness exceeding 0.5 mm, the presence of ulceration, histopathological evidence of mitotic figures and epithelioid cells, and neoplastic cells within the blood or lymphatic vessels of the tumor, as well as tumor-associated lymphangiogenesis [14, 16, 20, 21, 31–34]. The stage of advancement is assessed using the TNM classification system (Tab. I and II). Clinically suspicious pigmented lesions, as well as those that have developed recently or show signs of progression, should be excised and subjected to histopathological evaluation. A clinically suspicious pigmented lesion is characterized by asymmetry in pattern and color, multiple colors, the presence of gray and black color or structureless areas, polymorphic and feeding vessels, and a pattern of black dots (Fig. 4) [35]. Conjunctival melanoma may be amelanotic (Fig. 5). In the diagnosis of pigmented conjunctival lesions, the pattern analysis algorithm is a valuable instrument. It involves evaluating the presence of nine key suspicious features, including: the presence of more than two colors, color asymmetry, pattern asymmetry, vessel polymorphism, short vessels, linear vessel arrangement, a peripheral structureless area (distinct in color from the surrounding conjunctiva), a gray structureless area, and black dots (anywhere within the lesion). One point is assigned for the presence of each feature. If, after summing the points, the pigmented lesion receives a score equal to or greater than 3, the probability of diagnosing melanoma exceeds $p > 0.001$, and the lesion should be considered for surgical treatment [36].

The gold standard for treating conjunctival melanoma is surgical excision of the tumor, preceded by occlusion of the feeding

1. Clinical staging	Distant metastasis (M)
Primary tumor (T)	Mx Presence of distant metastasis cannot be assessed
T0 No evidence of primary tumor	M0 No distant metastasis
T(is) Melanoma confined to the conjunctival epithelium	M1 Distant metastasis
T1a ≤1 quadrant	
T1b >1 to ≤2 quadrants	
T1c >2 to ≤3 quadrants	
T1d >3 quadrants	
T2 Tumor of the non-bulbar conjunctiva	
T2a No caruncular, ≤1 quadrant	
T2b No caruncular, >1 quadrant	
T2c Any caruncular, ≤1 quadrant	
T2d Any caruncular, >1 quadrant	
T3 Any malignant conjunctival melanoma with local invasion	
T3a Globe	
T3b Eyelid	
T3c Orbit	
T3d Sinuses (ethmoid, maxillary)	
T4 Tumor invading the central nervous system	
Regional Lymph Nodes (N)	
Nx Regional lymph nodes cannot be assessed	
pN0 No regional lymph node metastasis (biopsy performed)	
cN0 No regional lymph node metastasis (biopsy not performed)	
pN1 Regional lymph node metastasis	

Tab. I. TNM clinical staging of conjunctival melanoma based on the AJCC Cancer Staging Manual.

1. Pathologic staging	Distant metastasis (pM)
Primary tumor (pT)	pMx Presence of distant metastasis cannot be assessed
pTx Primary tumor cannot be assessed	pM0 No distant metastasis
pT0 No evidence of primary tumor	pM1 Distant metastasis
pT(is) melanoma in situ (involving >75% of conjunctival epithelial thickness and/or presence of epithelioid cells and/or formation of nests)	Residual tumor
pT1 Invasive conjunctival melanoma	Rx Presence of residual tumor cannot be assessed
pT1a <0.5 mm in thickness	R0 No residual tumor
pT1b >0.5 mm but ≤1.5 in thickness	
T1c >1.5 mm in thickness	
pT2 Invasive conjunctival melanoma extending into nonbulbar conjunctiva	
pT2a ≤0.5 mm in thickness	
pT2b >0.5 mm but ≤1.5 in thickness	
pT2c >1.5 mm in thickness	
pT3 Melanoma invading the globe, eyelids, nasolacrimal duct, sinuses, or orbit	
pT4 Melanoma invading the central nervous system	
Regional Lymph Nodes (pN)	
pNx Regional lymph nodes cannot be assessed	
pN0 No regional lymph node metastasis	
pN1 Regional lymph node metastasis	

Tab. II. TNM pathological classification of conjunctival melanoma based on the AJCC Cancer Staging Manual.

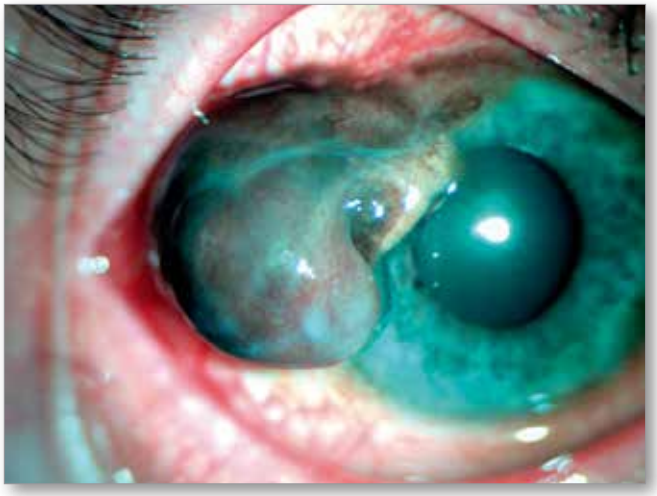

Fig. 4. Conjunctival melanoma.

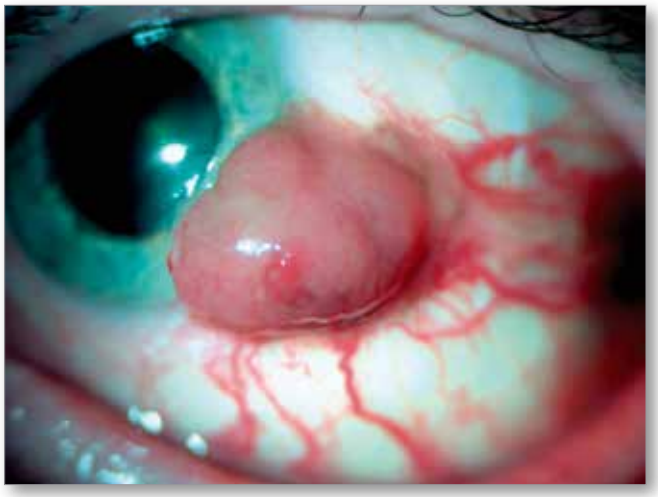

Fig. 5. Amelanotic conjunctival melanoma.

vessels, with a macroscopically clear margin of healthy tissue, followed by adjunctive local therapies such as chemotherapy, immunotherapy, or irradiation [21, 22, 23, 24]. Sentinel node biopsy should be considered (distant metastases occur in 50% of cases even in the absence of cancer cells in the regional lymph nodes). For lesions affecting multiple areas of the conjunctiva that cannot be excised in a single procedure, performing biopsies for histopathological verification (conjunctival mapping) is recommended. Adjunctive or alternative treatments include enucleation, exenteration, local chemotherapy (mitomycin-C or 5-fluorouracil), immunotherapy (interferon-alpha2b), brachytherapy (Ru-106, I-125, or Sr-90), proton radiotherapy, and external beam radiotherapy (EBRT) [14, 16, 19, 21, 22, 24, 30].

For the treatment of metastatic conjunctival melanoma, therapies typically used for disseminated cutaneous melanoma are implemented.

Given the high risk of local recurrence patients diagnosed with melanoma should be followed up ophthalmologically every few weeks following treatment. It is crucial to thoroughly examine the entire conjunctival sac, including the tarsal conjunctiva of the upper eyelid (following eyelid eversion). It is also important to document the patient's local condition through photography at each follow-up visit. Any new pigmented lesions that arise should be excised and verified histopathologically.

Patients who have undergone treatment for conjunctival melanoma metastases also require ongoing oncologic follow-up, including ultrasound examination of the regional lymph nodes.

Disclosure
Conflict of interests: none declared
Funding: no external funding
Ethics approval: Not applicable.

References:

1. Shields CL, Demirci H, Karatza E, et al.: *Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors*. Ophthalmology. 2004 Sep; 1 1 1(9): 1747–1754. doi: 10.1016/j.ophtha.2004.02.013. PMID: 15350332.
2. Shields CL, Shields JA: *Tumors of the conjunctiva and cornea*. Surv Ophthalmol. 2004 Jan-Feb; 49(1): 3–24. doi: 10.1016/j.survophthal.2003.10.008. PMID: 1471–1437.
3. Gupta Y, Gahine R, Hussain N, et al.: *Clinico-Pathological Spectrum of Ophthalmic Lesions: An Experience in Tertiary Care Hospital of Central India*. J Clin Diagn Res. 2017 Jan; 11(1): EC09-EC13. doi: 10.7860/JCDR/2017/23589.9230. Epub 2017 Jan 1. PMID: 28273971; PMCID: PMC5324416.

4. Romanowska-Dixon B, Jakubowska B: *Czerniak błony naczyniowej*. Atlas. Wydawnictwo Uniwersytetu Jagiellońskiego. Kraków 2015, wyd. 1.
5. Shields CL, Belinsky I, Romanelli-Gobbi M, et al.: *Anterior segment optical coherence tomography of conjunctival nevus*. Ophthalmology. 2011 May; 118(5): 915–919. doi: 10.1016/j.ophtha.2010.09.016. Epub 2010 Dec 13. PMID: 21146221.
6. Alzahrani YA, Kumar S, Abdul Aziz H, et al.: *Primary Acquired Melanosis: Clinical, Histopathologic and Optical Coherence Tomographic Correlation*. Ocul Oncol Pathol. 2016 Apr; 2(3): 123-127. doi: 10.1159/000440960. Epub 2015 Nov 12. PMID: 27390743; PMCID: PMC4911799.
7. Levecq L, de Potter P Jamart J: *Conjunctival nevi clinical features and therapeutic outcomes*. Ophthalmology. 2010 Jan; 117(1): 35–40. doi: 10.1016/j.ophtha.2009.06.018. Epub 2009 Nov 5. PMID: 19896191.
8. Oellers P Karp CL: *Management of pigmented conjunctival lesions*. Ocul Surf. 2012 Oct; 10(4): 251–263. doi: 10.1016/j.jtos.2012.08.002. Epub 2012 Aug 11. PMID: 23084146.
9. Dębicka-Kumela M, Romanowska-Dixon B, Karska-Basta I, et al.: *The Evaluation of the Malignant Characteristics of Conjunctival Lesions Based on the Dermatoscopic Algorithm*. Anticancer Res. 2021 Feb; 41(2): 895–903. doi: 10.21873/anticanres.14842. PMID: 33517295.
10. Shields CL, Shields JA: *Tumors of the conjunctiva and cornea*. Indian J Ophthalmol. 2019 Dec; 67(12): 1930–1948. doi: 10.4103/ijo.IJO_2040_19. PMID: 31755426; PMCID: PMC6896532.
11. Shields JA, Shields CL, Mashayekhi A, et al.: *Primary acquired melanosis of the conjunctiva: risks forprogression to melanoma in 311 eyes. The 2006 Lorenz E. Zimmerman lecture*. Ophthalmology. 2008 Mar; 115(3): 511––519.e2. doi: 10.1016/j.ophtha.2007.07.003. Epub 2007 Sep 20. PMID: 17884168.
12. 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; discussion 71–72. PMID: 18427595; PMCID: PMC2258121.
13. Lim LA, Madigan MC, Conway RM: *Conjunctival melanoma: a review of conceptual and treatment advances*. Clin Ophthalmol. 2013; 6: 521–531. doi: 10.2147/OPTH.S38415. Epub 2013 Mar 13. PMID: 23515569; PMCID: PMC3601642.
14. Asadi-Amoli F, Ghanadan A: *Survey of 274patients with conjunctival neoplastic lesions in Farabi Eye Hospital, Tehran 2006-2012*. J Curr Ophthalmol. 2015 Oct 31; 27(1–2): 37–40. doi: 10.1016/j.joco.2015.09.007. PMID: 27239573; PMCID: PMC4877714.
15. Honavar SG, Manjandavida FP: *Tumors of the ocular surface: A review*. Indian J Ophthalmol. 2015 Mar; 63(3): 187–203. doi: 10.4103/0301-4738.156912. PMID: 25971163; PMCID: PMC4448231.
16. Shields CL, Markowitz JS, Belinsky I, et al.: *Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases*. Ophthalmology. 2011 Feb; 118(2): 389–395. e1-2. doi: 10.1016/j.ophtha.2010.06.021. Epub 2010 Aug 17. PMID: 20723990.
17. Shields CL, Sioufi K, Alset AE, et al.: *Clinical Features Differentiating Benign From Malignant Conjunctival Tumors in Children*. JAMA Ophthalmol. 2017 Mar 1; 135(3): 215–224. doi: 10.1001/jamaophthalmol.2016.5544. PMID: 28125759.
18. Novais GA, Fernandes BF, Belfort RN, et al.: *Incidence of melanocytic lesions of the conjunctiva in a review of 10 675 ophthalmic specimens*. Int J Surg Pathol. 2010 Feb; 18(1): 60–63. doi: 10.1177/1066896908319775. Epub 2008 Jul 8. PMID: 18611943.
19. Brownstein S: *Malignant melanoma of the conjunctiva*. Cancer Control. 2004 Sep-Oct; 11(5): 310–316. doi: 10.1177/107327480401100505. PMID: 15377990.
20. Shields CL: *Conjunctival melanoma*. Br J Ophthalmol. 2002 Feb; 86(2): 127. doi: 10.1136/bjo.86.2.127. PMID: 1 1815331; PMCID: PMC1771015.
21. Volpini BMF, Maia M, Agi J, et al.: *Synchronous conjunctival melanoma and lentigo maligna melanoma*. An Bras Dermatol. 2017 Jul-Aug; 92(4): 565–567. doi: 10.1590/abd1806-4841.20176015. PMID: 28954115; PMCID: PMC5595613.
22. Shields CL, Chien JL, Surakiatchanukul T, et al.: *Conjunctival Tumors: Review of Clinical Features, Risks, Biomarkers, and Outcomes--The 2017 J. Donald M. Gass Lecture*. Asia Pac J Ophthalmol (Phila). 2017 Mar-Apr; 6(2): 109–120. doi: 10.22608/APO.201710. PMID: 28399347.
23. Romanowska-Dixon B, Jeger MJ, Coupland SE: *Onkologia okulistyczna*. Rozdział: *Nowotwory spojówki*. PZWL – Wydawnictwo Lekarskie: 80, Warszawa 2019.
24. Rakusiewicz K, Kanigowska K, Grajkowska W, et al.: *Surgical treatment of conjunctival nevi in pediatric patients*. Klinika Oczna/ Acta Ophthalmologica Polonica. 2019; 121(1): 29–33. DOI:10.5114/ko.2019.85213.
25. Furdova A, Pesko K, Strmen P, et al.: *Conjunctival nevus and melanoma*. Bratisl Lek Listy. 2007; 108(7): 287–291. PMID: 17972544.
26. Pogrzebielski A, Romanowska-Dixon B: *Czerniak spojówki*. Okulistyka po Dyplomie. 2011; tom I (0): 36–43.
27. Dębicka-Kumela M, Karska-Basta I, Markiewicz A, et al.: *Analiza kliniczna i histopatologiczna 312 guzów spojówki leczonych chirurgicznie*. Klin Oczna. 2019; 121(1): 41–46.
28. Cohen VM, Ahmadi-lari S, Hungerford JL: *Gastric metastases from conjunctival melanoma*. Melanoma Res. 2007 Aug; 17(4): 255–256. doi: 10.1097/CMR.0b013e3281c4a056. PMID: 17625457.
29. Albreiki DH, Gilberg SM, Farmer JP: *Conjunctival malignant melanoma: A rare variant and review of important diagnostic and therapeutic considerations*. Saudi J Ophthalmol. 2012 Apr; 26(2): 151–156. doi: 10.1016/j.sjopt.2012.02.006. PMID: 23960986; PMCID: PMC3729676.
30. Zhou C, Wang Y, Jia R, et al.: *Conjunctival Melanoma in Chinese Patients: Local Recurrence, Metastasis, Mortality, and Comparisons With Caucasian Patients*. Invest Ophthalmol Vis Sci. 2017 Oct 1; 58(12): 5452–5459. doi: 10.1167/iovs.17-22376. PMID: 29059312.
31. Jain P, Finger PT, Fili M, et al.: American Joint Committee on Cancer Ophthalmic Oncology Task Force. *Conjunctival melanoma treatment outcomes in 288 patients: a multicentre international data-sharing study*. Br J Ophthalmol. 2020 Sep 5: bjophthalmol-2020-316293. doi: 10.1136/bjophthalmol-2020-316293. Epub ahead of print. PMID: 32892167.
32. Esmaeli B, Wang X, Youssef A, et al.: *Patterns of regional and distant metastasis in patients with conjunctival melanoma: experience at a cancer center over four decades*. Ophthalmology. 2001 Nov; 108(11): 21012105. doi: 10.1016/s0161-6420(01)00782-5. PMID: 11713086.
33. Romanowska-Dixon B, Jakubowska B: *Nowotwory spojówki*. W *Onkologia Okulistyczna*; PZWL 2019: 49–104.
34. Romanowska-Dixon B: *Chirurgiczne leczenie zmian spojówki*. W *Chirurgia Okulistyczna*; PZWL 2021: 89–96.
35. Romanowska-Dixon B, Jakubowska B: *Conjunctival tumors*. W *Ocular Oncology* PZWL; 2020: 49–105.
36. Dębicka-Kumela M, Romanowska-Dixon B, Karska-Basta I, et al.: *Diagnostic Algorithm for Conjunctival Melanocytic Lesions*. Anticancer Res. 2021 Jun; 41(6): 3161–3167. doi: 10.21873/anticanres.15102. PMID: 34083311.

Reprint requests to:
Magdalena Dębicka-Kumela, PhD, MD
(e-mail: magdalena.debicka-kumela@uj.edu.pl)
Oddział Kliniczny Okulistyki i Onkologii Okulistycznej Szpitala Uniwersyteckiego w Krakowie
ul. Kopernika 38, 31-501 Kraków, Poland