Diagnostic Algorithm for Conjunctival Melanocytic Lesions

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Abstract. *Background/Aim: This study aimed to develop an algorithm allowing the differentiation between conjunctival melanoma and other melanocytic infiltrations of the conjunctiva, on the basis of a dermatoscopic examination. Patients and Methods: A total of 160 conjunctival pigmented lesions were studied (40 melanomas and 120 non-melanoma conjunctival infiltrations). The clinical characteristics of the tumours were assessed with the use of dermatoscopic characteristics as described by Kittler, and with taking into consideration the typical characteristics of conjunctival lesions. Results: On the basis of modified dermatoscopic criteria, an algorithm was generated consisting of an assessment of the presence of 9 suspicious characteristics, e.g. more than two colours, colour asymmetry, pattern asymmetry, vascular polymorphism, presence of short vessels, linear vascular pattern, the presence of a peripheral structureless area, the presence of a grey structureless area and black dots in any part of the lesion. The presence of any of these characteristics scores 1 point. If a melanocytic lesion scores ≥3 points, the probability of diagnosing melanoma is on the level of p>0.001. Conclusion: The use of the proposed algorithm, based on modified dermatoscopic characteristics, may be a valuable tool for the diagnosis of conjunctival melanoma.*

Conjunctival melanoma (CMM) is a rare tumour: it is approximately 500 times less frequent than skin melanoma (1). It constitutes 1.6% of all non-cutaneous melanomas and 1-5%

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of all ocular melanomas (2, 3). The incidence of CMM has significantly increased in the USA and Europe over the recent years. It is estimated that the increase amongst white males is 295% within 27 years (4). Only rare cases have been reported in children (5, 6). The mortality rate of patients with CMM is 8% within 5 years, 13% within 8 years, and 30% within 10 years (1, 7-9). The prognosis of CMM is slightly better than that of melanoma of other mucosal membranes, where the 5-year survival rate is 26% (10). This fact is related to the presence of CMM on a visible part of the body, which allows for early diagnosis. Conjunctival melanoma can spread through the lymphatic system and bloodstream, or it can undergo direct extension to the globe and orbit (11, 12). Patients with initial lymph node metastases have better prognosis than those initially presenting with systemic metastases (1). Conjunctival melanoma also has a high recurrence tendency (19-45% within 5 years, 26-59% within 10 years and 65% within 15 years of follow-up) (2, 4, 7, 12-15). The median interval of recurrence varies between 11 and 17 months (4, 12-15). A poorer prognosis (higher rates of recurrence and metastases), apart from a non-bulbar tumour location, the presence of mitotic figures, epithelioid cells, lymphatic or vascular invasion, and tumour lymphangiogenesis in the histopathological examination, are typical of tumours with a thickness greater than 0.5 mm and with ulceration (1, 4, 8, 9, 14). Therefore, it is essential to recognise CMM precursors at an early stage. A golden standard in the treatment of CMM is wide local excision (according to some authors in combination with cryotherapy to the margins and alcohol corneal epitheliectomy). Alternative or adjuvant treatments include enucleation, exenteration, topical chemotherapy (mitomycin-C, interferon-alfa2b or 5-fluorouracil), plaque brachytherapy (Ru-106 or Sr-90), proton beam radiotherapy, and external beam radiotherapy (EBRT) (2, 4, 9, 16-18). CMM must be differentiated from other melanocytic conjunctival infiltrations, such as naevi, and primary acquired melanosis (PAM), which may be CMM precursors. The correct differential diagnosis between melanoma and other melanocytic conjunctival lesions is of key significance for avoiding delays in diagnosing

Table I. *Demographic data depending on histopathological diagnosis.*

Demographic data	Histopathological diagnosis		
	Melanoma (malignant tumour) (n=40)	Nevus or PAM without atypia (benign lesion) (n=80)	PAM with atypia (premalignant lesion) (n=40)
Age	62.7±17.7	39.8±20.4	59.9±17.1
Children	0 (0.0)	12 (15.0)	0 (0.0)
Gender			
Male	18 (45.0)	49 (61.2)	16 (40.0)
Female	22 (55.0)	31 (38.8)	24 (60.0)

melanoma, as this worsens the prognosis. Early stages of CMM, consisting especially of flat lesions, often pose diagnostic challenges, because at that time they share some features with benign mucosal lesions. As an incisional diagnostic biopsy of CMM may increase the risk of local recurrence of the tumour, it is necessary to search for diagnostic algorithms which would facilitate quicker diagnostics, particularly of small cancer lesions (2, 14). The objective of our paper was to generate a diagnostic algorithm, which would differentiate between melanomas and other melanocytic conjunctival infiltrations. This would be mainly based on the criteria applied in dermatoscopy, but also taking into consideration the characteristics that are only typical of conjunctival lesions (19, 20).

Patients and Methods

Patients and settings. The study was performed on consecutive non-selected pigmented melanocytic conjunctival lesions, qualified for surgical excision. It comprised 160 melanocytic conjunctival lesions in 158 patients (median age 50.5 years; age range=5-87 years). Among the examined tumours, a histopathological assessment confirmed 40 malignant tumours (conjunctival CMM) as well as 120 non-melanoma melanocytic conjunctival lesions (40 cases of each category: naevus, PAM without atypia and PAM with atypia). There were 83 tumours in men and 77 in women. Patients were diagnosed and treated in the Department of Ocular Oncology and Ophthalmology between 2015 and 2018. The detailed characteristics of the examined group depending on individual histopathological categories are presented in Table I.

Examined lesion diagnosis. Each conjunctival lesion, which was qualified for excision, was re-assessed by 3 independent ophthalmologists, specialising in ocular oncology, according to the previously described (19) protocol of ophthalmological examination developed for the purposes of this work. The tumours were described on the basis of eye biomicroscopy, without preliminary diagnosis. The description employed the algorithm used in dermatoscopy as described by Kittler (20). Then, a colour schematic drawing of each tumour was made with a description and a colour photo with 8, 12, and 20-fold magnification. The images of the

melanocytic lesions were obtained using a slit lamp with an SL-imaging system, by a fully integrated digital camera SL Cam 5.0 (The Carl Zeiss Meditec Group, Jena, Germany). The results of the assessment were close to the contactless dermatoscopy as a diffusor filter with 8, 12, and 20-fold magnification was used. All excised lesions were examined by a pathologist with expertise in melanocytic lesions.

Clinical data. The demographic data of the patients were recorded. Then, the clinical picture of the conjunctival infiltrations was evaluated, taking into consideration the degree of their elevation (differentiating between flat, elevated, partly elevated, and flat lessions). The type and number of colours (different from the surrounding conjunctiva) of each of the infiltrations were recorded. The presence of colours was also recorded as brown (differentiating into light and dark brown), black, white, pink, grey or blue. Each lesion was scored using dermatoscopic patterns, as described by Kittler: dots, globules, pseudopods, circles, lines (the pattern is described when its core element involves a significant part of the melanocytic lesion). A structureless pattern was defined as the lack of any of the above described elements on the predominant area of the lesion (20). Then, the presence of chaos was assessed (the asymmetry of pattern or colour) in the case of all infiltrations, characterized by more than one pattern and/or colour. In addition, the vascular pattern within the infiltration was described, taking into consideration only the vessels with a different pattern from the adjacent conjunctiva and the vascular patterns described by Kittler: dots, globules, lines. The presence of short and long vessels was recorded (and short vessels were defined as those whose length is only slightly larger than their width). The presence of more than one dominating type of vessel was described as a polymorphous vessel. It was then verified whether there was any evidence of malignancy (clues of malignancy) in the melanocyte lesion as described by Kittler, such as a grey structureless area, an eccentric structureless zone (any colour except the conjunctiva), polymorphous vessels, and segmental pseudopods (20). Also, the characteristics added in our study were described, comprising cysts, peripheral feeder vessels, and black dots on the entire surface of the lesion (not only located peripherally) (19).

Statistical analysis. Continuous data are presented as a mean value and standard deviation (SD). Categorical data are presented as a percentage. Normal distribution was verified with the Kolmogorov-Smirnov test. Continuous data from two groups were compared with

Table II. *The comparison of the results of dermatoscopic assessment for the group with melanoma and non-melanoma melanocytic conjunctival lesions with consideration of the specificity and sensitivity of a given property.*

	Non-melanoma melanocytic conjunctival lesions (n=120) (controls)	Conjunctival melanoma (n=40) (cases)	*p*-Value	Sensitivity (%)	Specificity (%)
Elevated lesion	23 (19.2)	15 (37.5)	0.018	37.5	80.8
Partly elevated lesion	3 (2.5)	14 (35.0)	**<0.001**	35.0	97.5
Pattern					
Number of patterns					
1	31 (25.8)	5 (12.5)			
≥2	89 (74.2)	35 (87.5)			
Pattern asymmetry	14 (11.7)	30 (75.0)	**<0.001**	**75.0**	**88.3**
Type of pattern					
Lines	52 (43.3)	15 (37.5)	0.517	37.5	56.7
Dots	104 (86.7)	31 (77.5)	0.167	77.5	13.3
Papules	5 (4.2)	5 (12.5)	0.123	12.5	95.8
Circles	6 (5.0)	1 (2.5)	0.681	2.5	95.0
Pseudopods	1 (0.8)	7 (17.5)	**<0.001**	17.5	99.2
Structureless	53 (44.2)	39 (97.5)	**<0.001**	**97.5**	**55.8**
Colour					
Number of colours					
1	60 (50.0)	2 (5.0)			
2	44 (36.7)	11 (27.5)			
3	15 (12.5)	17 (42.5)			
4	1 (0.8)	9 (22.5)			
5	0 (0.0)	0 (0.0)			
6	0 (0.0)	1 (2.5)			
Colour asymmetry	14 (11.7)	31 (77.5)	**<0.001**	**77.5**	**88.3**
Light brown	81 (67.5)	25 (62.5)	0.562	62.5	32.5
Dark brown	65 (54.2)	27 (67.5)	0.140	67.5	45.8
Black	29 (24.2)	23 (57.5)	**<0.001**	**57.5**	**75.8**
White	0 (0.0)	6 (15.0)	**<0.001**	15.0	100.0
Grey/blue	11 (9.2)	19 (47.5)	**<0.001**	47.5	90.8
Pink	11 (9.2)	16 (40.0)	**<0.001**	40.0	90.8
Blood vessels					
Symmetry of vascular pattern					
Polymorphic	7 (5.8)	20 (50.0)			
Monomorphic	21 (17.5)	6 (15.0)			
None	92 (76.7)	14 (35.0)			
Type of vascular pattern					
Dots	6 (5.0)	16 (40.0)	**<0.001**	40.0	95.0
Papules	2 (1.7)	4 (10.0)	0.035	10.0	98.3
Lines	26 (21.7)	25 (62.5)	**<0.001**	**62.5**	**78.3**
The presence of short vessels	15 (12.5)	24 (60.0)	**<0.001**	**60.0**	**87.5**
The presence of long vessels	19 (15.8)	18 (45.0)	**<0.001**	45.0	84.2
Clues to malignancy and other special properties					
Peripheral structureless area	4 (3.3)	11 (27.5)	<0.001	27.5	96.7
Grey structureless area	11 (9.2)	20 (50.0)	**<0.001**	**50.0**	**90.8**
Black dots	29 (24.2)	22 (55.0)	**<0.001**	**55.0**	**75.8**
Segmental pseudopods	1 (0.8)	8 (20.0)	**<0.001**	20.0	99.2
Peripheral feeder vessels	4 (3.3)	16 (40.0)	**<0.001**	40.0	96.7
Cysts	14 (11.7)	0 (0.0)	0.022	0.0	88.3

Bold values indicate statistical significance.

the Student's *t*-test or the Mann-Whitney *U*-test, depending on the distribution. More than two groups were compared with the univariate analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) test or with the Kruskall-Wallis test depending on the distribution. Categorical data were compared with the Chi-square test and Fisher's exact test. The receiver operating characteristic (ROC) curve was performed to assess the area under the curve (AUC), as well as the sensitivity and specificity of our melanoma scoring. A *p*-value less than 0.05 was considered statistically significant. Data were analysed with the use of SPSS software v.21 (IBM, Armonk, NY, USA).

The authors declare that this investigation was carried out according to the rules of the Declaration of Helsinki of 1975 (revised in 2013).

Results

Table II contains the results of the study on the basis of the guidelines used in dermatoscopy. The comparative analyses of the results of the examinations carried out on the group of patients with conjunctival melanoma versus the control group (other melanocytic conjunctival infiltrations) revealed many significant results (Table II). In both groups, there were completely elevated infiltrations, yet CMM was more often found only in partly elevated tumours ($p<0.001$). The studied groups did not differ from each other with regards to the number of patterns observed; in both groups the dominating pattern comprised dots and lines. In melanoma, however, pattern asymmetry was more frequent ($p<0.001$); similarly to the structureless pattern and pseudopods ($p<0.001$). In both study groups, the dominating colour was light and dark brown, CMM however, had a larger average number of colours and colour asymmetry ($p<0.001$) and also more frequently contained the colour black, white, grey, or blue and pink ($p<0.001$). In the CMM group, evidence of malignancy comprising a peripheral structureless area, a grey structureless area, black dots (not only located peripherally but also on the entire area of the tumour), as well as segmentally located pseudopods and polymorphous vessels ($p<0.001$) were statistically more frequent. Cysts were more typical for non-melanoma conjunctival infiltrations; their presence was found in none of the cases of CMM, yet this was not statistically significant. The control group of non-melanoma tumours did not have visible vascularisation, and if visible vessels existed, they rather had a homogenous pattern (monomorphic) ($p<0.001$). In the case of CMM, characteristics such as visible vascularisation with the presence of both short and long vessels as well as polymorphous and peripheral feeder vessels were seen more frequently ($p<0.001$).

With the use of statistical analysis tools, we generated a new algorithm for the diagnosis of melanoma in the case of melanocytic conjunctival lesions (Table III). Each of the following characteristics score 1 point: the presence of more than two colours, colour asymmetry, pattern asymmetry, vascular polymorphism, the presence of short vessels, a linear

Table III. *The list of the properties evaluated in algorithm for pigmented conjunctival lesions. A lesion is considered as suspicious and should be removed if the score is ≥3.*

Characteristics of algorithm	Points
More than two colours	1
Colour asymmetry	1
Pattern asymmetry	1
Polymorphous vessels	1
Vessels lines pattern	1
Short vessels	1
Eccentric structureless zone	1
Grey structureless pattern	1
Black dots	1

vascular pattern, the presence of a peripheral structureless area (in any colour different from the colour of the surrounding conjunctiva), the presence of grey structureless area and black dots (in any part of the lesion) (Figures 1 and 2).

The ROC for melanoma is illustrated in Figure 3. The diagnostic strength of AUC was 0.918 ($p<0.001$). For the cut-off point of 3.0, the sensitivity of the test was 90%, and specificity 83%.

The scoring of the presence of specific properties indicative of malignancy in various types of melanocytic conjunctival lesions is presented in Table IV.

On the basis of the scoring, only the differentiation between the diagnosis of PAM with atypia and melanocytic naevus was uncertain ($p=0.681$); in all other cases (the differentiation between PAM without atypia and PAM with atypia or naevus or melanoma as well as melanoma and PAM with atypia or naevus) it was very certain ($p<0.001$).

Discussion

In dermatology, there are many dermatoscopic algorithms that facilitate the diagnosis of skin melanoma. It is known, that a dermatoscopic picture depends on the tumour location on the skin. For mucosal membranes (other than conjunctiva), the literature describes the presence of many dermatoscopic characteristics suggesting the presence of melanoma, such as a multicomponent pattern, an irregular pattern, the presence of white, grey or blue colour, particularly in connection with a structureless area, atypical network, polychrome, irregular dots or grey granulation, atypical or irregular vessels or blue-white vail (2, 21-25). These data, however, cannot be used for the diagnosis of conjunctival melanoma, based on the differences in structure compared to other mucosal membranes. To the best of our knowledge, so far there has not been any simple algorithm for the diagnosis of the early form of conjunctival melanoma. Shields *et al.*, in their study of a large group of conjunctival tumours, observed that the
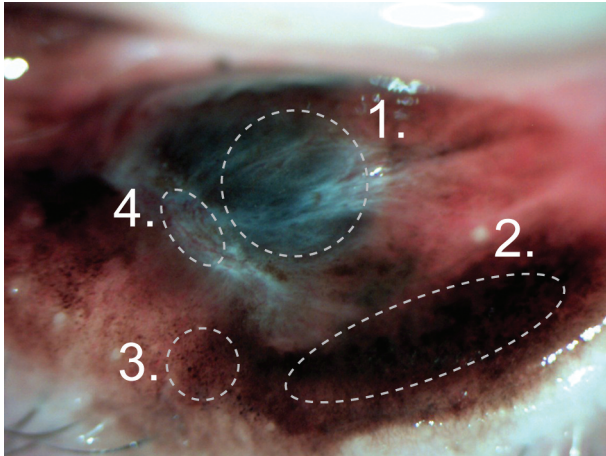
Figure 1. *Conjunctival melanoma – with more than 2 visible colours (grey, white, pink and dark brown), partly flat and partly elevated infiltration [1-grey structureless; 2-peripheral structureless area (brown colour); 3-black dots; 4-vessels lines].*
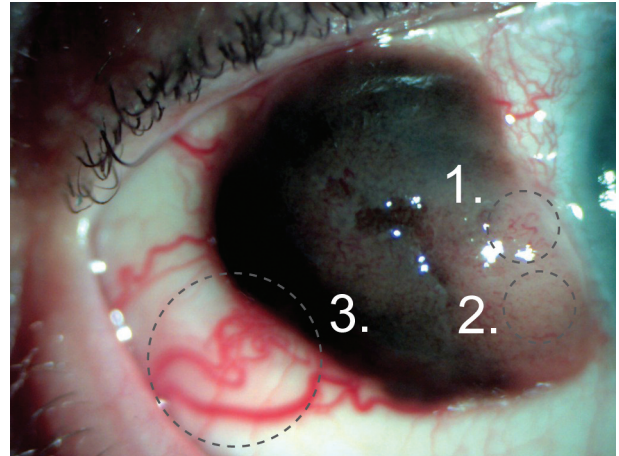

Figure 2. *Conjunctival melanoma – visible polymorphous vessels (1-linear long vessels; 2-short vessels; 3-feeder vessels).*

greatest relative risks for melanoma (vs. PAM) were older age, tarsal location, lack of pigmentation, greater than 1 mm thickness, feeder vessels, cysts, intrinsic vessels, and haemorrhaging (26). However, many of these characteristics are related to advanced cancer. Nevertheless, little is known about the possible role of dermatoscopic algorithms in the diagnosis of conjunctival melanoma. In the first study by Cinotti *et al*. concerning the dermatoscopic features of a series of conjunctival lesions, the authors could not find any dermatoscopic criteria allowing for the differential diagnosis of melanoma, except for the higher presence of a grey colour in CMM than in naevi (27). Tosi *et al*. described 39 conjunctival pigmented tumours that were imaged with a noncontact camera that provided digital images at 16× magnification, and evaluated many dermatoscopic parameters using a dedicated software (digital surface dermoscopy). CMM was found to be larger, darker, and with more internal contrast and blue-grey colour than benign lesions (24).

However, no large-scale study has been performed to define the dermatoscopy criteria for conjunctival melanoma. We evaluated whether the algorithms commonly used for distinguishing melanoma from benign lesions of the skin are also applicable to lesions on the conjunctiva. We managed to confirm earlier reports about the more frequent presence of grey or blue colour in the case of conjunctival melanoma. Additionally, we showed that other properties of the pigmentation of a melanocytic tumour such as the presence of a black, white, and pink colour, and a larger average number of colours and colour asymmetry point to its malignant character. We also described reliable dermatoscopic patterns typical of CMM, such as a structureless pattern and pattern
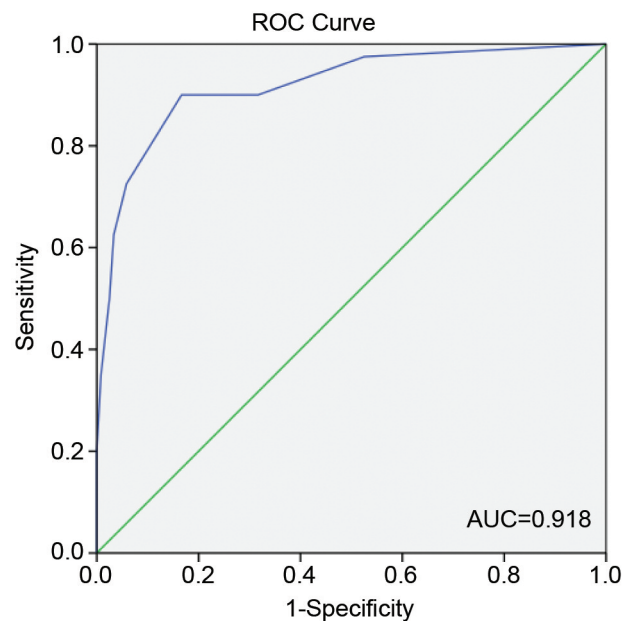

Figure 3. *Algorithm presenting receiver operating characteristic (ROC) curve for the diagnosis of melanoma. The ROC curve was performed to assess the area under the curve (AUC), sensitivity, and specificity of our melanoma scoring. A p-value <0.05 was considered statistically significant.*

asymmetry. Furthermore, we documented evidence of malignancy comprising a peripheral structureless area, a grey structureless area, black dots (not only located peripherally but also on any part of the tumour), and segmentally located pseudopods, which are all typical of CMM. In addition, we

Table IV. *Quantitative results for the presence of specific properties indicative of malignancy (scoring) w in various types of conjunctival melanocytic lesions.*

	1 PAM without atypia (n=40)	2 PAM with atypia (n=40)	3 Naevus (n=40)	4 Melanoma (n=40)	*p*-Value
Scoring	0.1±0.4	1.7±1.5	1.6±1.6	5.3±2.4	<0.001

observed the more frequent presence of visible vascularisation of the lesion in melanoma as compared with benign melanocytic infiltrations of the conjunctiva. In CMM, both short and long vessels as well as polymorphous and peripheral feeder vessels were presented.

We also created a simple and reliable diagnostic algorithm for detecting CMM in its early stage. The algorithm assesses the presence of 9 suspicious characteristics, which are referred to in Table III. Each characteristic scores 1 point. If the clinical assessment of a given melanocytic lesion scores ≥ 3 points, the probability of diagnosing melanoma is on the level of *p*>0.001.

The use of the proposed algorithm that is based on dermatoscopic characteristics appears to be a valuable tool for the diagnosis of conjunctival melanoma. However, further larger collaborative studies are needed to better validate our conjunctival melanoma diagnostic algorithm.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

M.D-K.: Conceptualization, methodology, investigation, data curation, writing - original draft, visualization, formal analysis; B.R-D.: conceptualization, methodology, investigation, data curation, writing - review & editing; J.K.: methodology, writing - review & editing, investigation, visualization; I.K-B.: methodology, writing -review & editing, investigation; W.P-M.: writing- review & editing, data curation, investigation; A.M.: conceptualization, methodology, investigation, supervision; writing - original draft; writing - review & editing; project administration, formal analysis, data curation. All Authors have reviewed the article and approved the submitted version.

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