A Multicentre Study Validates the WHO 2022 Classification for Conjunctival Melanocytic Intraepithelial Lesions with Improved Clinical and Prognostic Information

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Introduction

Several terminologies and grading systems have been proposed for Conjunctival Melanocytic Intraepithelial Lesions (C-MIL; Fig 1)[1-4]. In 2018, the 4th edition of 'World Health Organisation (WHO) Classification of Eye Tumours' proposed a C-MIL classification[4], simplifying the grading of these lesions but capturing their risk of disease progression to invasive melanoma. This system was validated in 2021 via a multicentre study examining H&E sections only[5]; however, slight weaknesses led to it being revised further for the 5th 'WHO Classification of Eye Tumours' in 2022[6].

Aims

1) To validate the WHO 2022 Classification of C-MIL.
2) To ensure reproducibility between pathologists in scoring these difficult lesions.
3) Guide treating clinicians in the management of these lesions.

Materials & Methods

- Archives were searched for C-MIL in three Ophthalmic Pathology study centres [Fig 2]. All adequate conjunctival biopsies included were stained with H&E, Melan-A (clone A103; AgilentDako), SOX10 (clone EP268; Cell Marque), and PRAME (clone QR005; ready to use; Anatopath).
- The slides were digitised on the SmartZoom platform and independently scored by 4 ocular pathologists from the three study centres, using the WHO 2022 classification[6] to reach a consensus score [Fig 3]. Access was subsequently provided to 14 additional pathologists from 8 countries.
- All results were anonymously collated for independent statistical analysis.

Results

- Evaluated were 105 cases from 97 patients (60 ♀, mean 62years; 37 ♂, mean 67years; 91% Caucasian). There were 28/105 benign melanoses, 13 Low-grade C-MIL; 37 High-grade C-MIL; and 27 melanoma in-situ. When using this 4-tiered grading system, 93% observers showed fair-to-moderate agreement (Kappa-statistics). With a simpler 3-tiered system (combining High-grade C-MIL and melanoma in-situ) [Table 1], 93% showed moderate-to-substantial agreement.
- The agreement level between the consensus panel and participating pathologists was similar across lesion types for both systems, with Low-grade C-MIL being the most diagnostically challenging [Table 2].
- Recurrence rates and development of invasive melanoma for High-grade C-MIL (3-tiered system) were 34% and 47%, [Table 3] respectively versus melanoma in-situ alone (4-tiered): 55% and 74%, respectively.
- The immunostains SOX10 and Melan-A were the most preferable across all grades of C-MIL. PRAME was used more frequently for the High-grade lesions, singly or in combination.

Conclusions

This large international collaborative study is the first to undertake a comprehensive review of C-MIL to validate the 5th WHO 2022 Classification. The simple 3-tiered system was found to have substantial interobserver agreement compared to the previous 2018 WHO scheme and good reproducibility. The combination of SOX10 and Melan-A was found to be the most useful across all grades of C-MIL. This classification provides good prognostic accuracy (recurrence risk and development of invasive melanoma). Importantly, it facilitates decision-making for the treating clinician as to which patients can be observed versus those requiring active treatment. It is recommended that this classification system be adopted by diagnostic labs worldwide.

References

1.Folberg R, McLean IW, Zimmerman LE. Primary acquired melanosis of the conjunctiva. Hum Pathol 1985;16(2): 129–135. 2. Damato B, Coupland SE. Management of conjunctival melanoma. Exp Rev Anticancer Ther 2009;9(9):1227–1239. 3.Jakobiec FA. Conjunctival primary acquired melanosis: is it time for a new terminology? Am J Ophthalmol 2016; 162:3–19. 4. Eberhart CG, Coupland SE, Folberg R, et al. Conjunctival melanocytic intraepithelial neoplasia. In: Grossniklaus HE, Eberhart CG, Kivela TT, eds. WHO Classification of Tumours of the Eye. 4th ed. Lyon, France: International Agency for Research on Cancer; 2018:31–33. 5. Milman T, Eiger-Moscovich M, Henry RK, et al. Validation of the Newly Proposed World Health Organization Classification System for Conjunctival Melanocytic Intraepithelial Lesions: A Comparison with the C-MIN and PAM Classification Schemes. Am J Ophthalmol. 2021;223:60-74. 6. Coupland SE, Milman T, Verdijk RM, et al. Conjunctival Melanocytic Intraepithelial Lesions. In: WHO Classification of Tumours Editorial Board. Eye tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2023. (WHO classification of tumours series; 5th ed.; vol. 13).

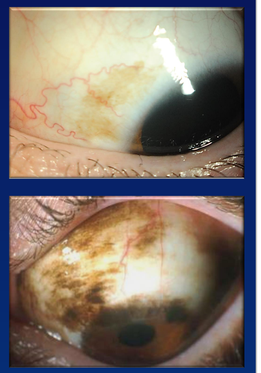


Fig 1: Low grade C-MIL (top); High grade C-MIL (bottom)

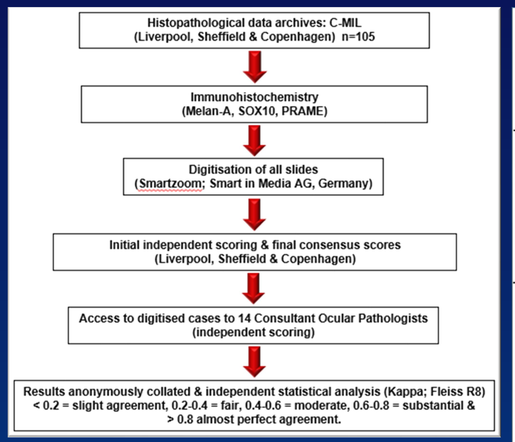


Fig 2: Methods workflow

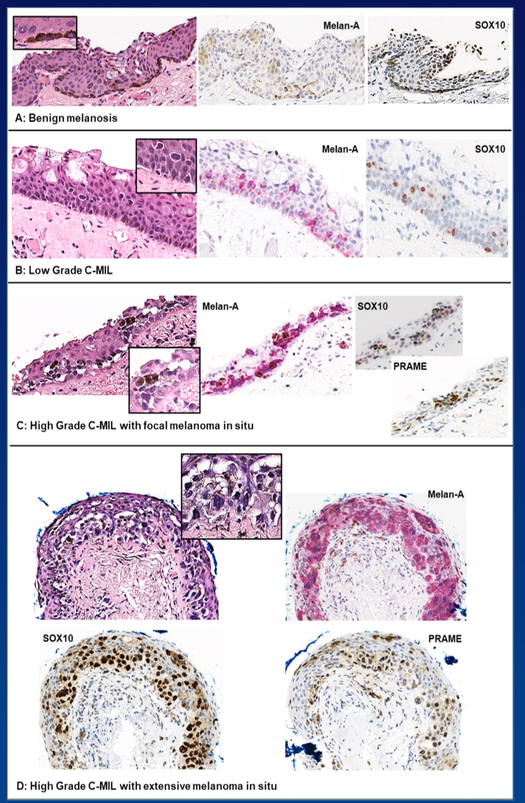


Fig 3: Histomorphological & immunohistochemical scoring of C-MIL

Observer	Kappa	Lower 95% CI	Upper 95% CI	Kappa for 3-grade system significantly higher than for 4-grade system
1	0.774	0.627	0.920	Yes
2	0.358	0.136	0.480	No
3	0.714	0.574	0.854	Yes
4	0.444	0.316	0.573	Yes
5	0.593	0.446	0.741	Yes
6	0.604	0.466	0.743	Yes
7	0.544	0.412	0.677	No
8	0.601	0.463	0.739	No
9	0.651	0.510	0.792	Yes
10	0.586	0.452	0.719	Yes
11	0.670	0.525	0.815	Yes
12	0.673	0.524	0.823	Yes
13	0.590	0.448	0.732	Yes
14	0.427	0.296	0.559	No

Table 1: Kappa statistics for the 14 observers compared with the consensus diagnosis in the 3-grade system

	Participating pathologists' responses (N=14)	
Consensus grades (N=4)	% Agreement	% Disagreement
Benign n=28	74.5	25.5
LG C-MIL n=13	38.7	61.3
HG C-MIL n=37	55.5	44.5
In-situ n=27	63.8	36.2
HG C-MILc n=64	85.4	14.6

Table 2: Comparison of C-MIL agreements between the consensus and participating pathologists

Consensus grade	No re-currence	Re-currence	% Re-currence	No IM	IM	% IM
Benign	28	0	0	28	0	0
LG C-MIL	12	1	8	13	0	0
HG C-MILc	42	22	34	34	30	47

Table 3: Outcome of developing local recurrence and developing invasive melanoma (IM) with the 3-grade system

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The ROYAL COLLEGE of OPHTHALMOLOGISTS RCOphth Annual Congress 20-23 May 2024, ICC Belfast