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Review

Conjunctival Melanoma: A Clinical Review and Update

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Simple Summary: Conjunctival melanoma (Co-M) is a rare and aggressive eye surface cancer. It is often misdiagnosed or overlooked leading to late diagnosis. Co-M can cause sight loss and even eye loss impacting quality-of-life. The numbers of new cases globally are rising at alarming rates. There is no standard treatment for Co-M and management varies between eye cancer centres. In ~25% the cancer spreads elsewhere in the body, which can lead to death. The aim of this review is concisely present what is currently known about Co-M presentation, its development and progression, clinical management and outcomes, and finally summarise future directions for research into novel therapies.

Abstract: Conjunctival melanoma (Co-M) is an aggressive, invasive eye and eyelid cancer. Its global incidence of ~1 in a million is increasing at a rate ratio of ~1.4, but this rises sharply in over 65-year-olds. Although rare, Co-M has a devastating impact on the lives of those who develop it. Co-M is often misdiagnosed or overlooked leading to vision loss either from destructive effects of the tumour or side effects of therapy, facial disfigurement from radical surgery, and death from metastases. Due to its rarity, there is limited evidence for diagnosis and management; hence, there is no standardised treatment and not all cases are referred to a specialised ocular oncology centre. Recent progress in cancer immunology and genetics have revolutionised treatment of cutaneous melanoma, which share some similarities to Co-M. A better understanding of Co-M and its precursor lesions is urgently needed to lead the development of novel targeted and immunotherapies both for local tumour control and disseminated disease. This review aims to provide a comprehensive clinical overview of the current knowledge of Co-M, its epidemiology, pathogenesis, presentation, diagnosis, management, and recent advances in novel biological therapies for personalised treatment of this disease.

Keywords: conjunctival melanocytic intraepithelial lesions; conjunctival melanoma; ocular oncology; targeted therapy; immunotherapy

1. Introduction

Conjunctival melanoma (Co-M) is a rare, aggressive invasive ocular surface cancer, which is often misdiagnosed or overlooked and causes significant visual disabilities, poor quality of life and even death from metastases. They occur most commonly in fair-skinned populations, with the overall incidence being approximately 0.46 cases per 1,000,000 persons per year [1,2], representing around 0.25% of melanomas at all sites and 5% of all ocular melanoma. It is the second most prevalent malignancy of the conjunctiva after squamous cell carcinoma [3] originating from the basal melanocytes in the conjunctival epithelium. The majority (~70%) of Co-M cases develop from conjunctival melanocytic intraepithelial lesions (C-MIN/ PAM with atypia), while others arise from pre-existing nevi or de novo [3,4].

Previous studies have often grouped Co-M with uveal melanoma as an ocular melanoma: the latter is the most common primary intraocular malignancy in adults, arising in the choroid, ciliary body or iris; however, uveal melanoma is embryologically, biologically and clinically very different to Co-M [5–9]. Unlike uveal melanoma, Co-M is a mucosal melanoma with histological and functional similarities to cutaneous melanoma [10,11] with similar genetic alterations. These include UV-related driver mutations in the BRAF, NF1 and RAS genes and copy number variations [6,12–19]. BRAF and NRAS mutations are present in ~30% and ~14–25% of Co-M, respectively, with the NRAS mutant Co-M being associated with higher metastatic risk [16]. Transcriptomic studies of Co-M that have focussed on the immune tumour microenvironment have also demonstrated high PDL1-expression, and a transcriptomic subtype enriched with immune genes (immune cell-types) [12,20,21].

Clinically Co-M most often presents in the bulbar conjunctiva, near the limbus, but can affect any part of the conjunctiva and even invade the neighbouring structures in advanced cases [4,22]. Lesions vary from amelanotic to brown pigmented or even black in colour. There is no standardised treatment; however, management includes: surgical excision +/- adjuvant cryotherapy, topical chemotherapy, brachytherapy, proton beam radiotherapy or photon external beam radiation, and in advanced cases with local tissue invasion - radical orbital exenteration [18,22–27]. Postoperative complications and tumour recurrence rates are high (33–45%), warranting life-long follow-up [4,28–31]. Metastases to lymph nodes are common (~25%) but may also involve the liver, lungs and brain, with ~27% 5-year disease-specific mortality rate [32,33].

Despite recent successes with targeted and immuno-therapies in cutaneous melanoma, data on Co-M treated with similar therapies (anti-BRAF/anti-MEK/anti-PDL1) are promising but limited, stemming from single patient or small case series with inoperable or advanced disease prior to surgery [34–38].

This review article aims to summarise the current understanding of Co-M and explore new advancements in the knowledge of Co-M pathophysiology and its treatment developments.

2. Epidemiology and pathogenesis of Co-M

The incidence of Co-M has increased over the last 5 decades [14,39] and ranges from 0.3 to 0.8 per million per year, being highest in Northern Europe and North America. The estimated number of new cases per year is 130 in the USA and 320 in Europe [18]. Populations of Asian or African descent are less commonly affected [2,40–43]. A study in the US found that fair skinned people had the highest incidence rate of Co-M, comprising 91.2% of cases compared to 2.4% in patients of Afro-Caribbean descent [44]. However, with majority of data coming from predominantly North America or Europe, there is very limited data on other ethnic groups. Co-M mainly affects patients in their 5th or 6th decades and above; it is rare in children and there is no gender predilection [14,39,40,45,46]. The disease specific survival rate for Co-M is estimated to be 82.9% for 5 years and 69.3% for 10 years [30,40].

Although the incidence of Co-M is substantially lower than cutaneous melanoma, if incidence is adjusted to tissue surface area, the incidence is similar. A study from the USA estimated the incidence of Co-M to be 0.4 per million persons/year and the incidence of cutaneous melanoma to be at 153.5/million persons per year [47]. The average skin area for an average human adult is 1.7m² [48] and the conjunctiva area per eye is 17.6cm² [49]. If the incidence of each melanoma is now calculated proportionately to the area, the incidence for cutaneous melanoma would be approximately 90 per million m² of skin per year, and for Co-M incidence estimated at 113 per million m² of conjunctiva per year [18]. Importantly, this puts Co-M in perspective considering the conjunctival size and although it shares similarities with skin melanoma, is hugely under researched in comparison [10].

Driver-mutations and copy-number variations in multiple chromosomes have been described in Co-M, with high-frequency mutations in NF1 (33–50%), BRAF (29–46%), and NRAS mutations (11–26%) and ATRX (25%) genes [6,12–17,50–54]. The latter often occurs together with an NF1 mutation [13]. NRAS mutations are associated with higher metastatic risk [13,17]. TERT promoter mutations have also been identified in up to 54% of Co-M [13,17,55,56] and even in PAM with atypia (~8%) [57]. Cisarova et al, demonstrated that the TCGA-proposed genomic classification of cutaneous melanoma

(defined by the most frequently mutated genes: BRAF, NF1, RAS and triple wild-type) was also applicable to Co-M [12]. A summary of the common gene mutations is presented in Table 1.

Table 1. Common genetic mutations in conjunctival nevi, primary acquired melanosis (PAM) without atypia, PAM with atypia, and conjunctival melanoma (Co-M).

	Conjunctival nevi (%)	PAM without atypia (%)	PAM with atypia (%)	Prevalence in Co-M (%)
BRAF				4/15 (27%) (Beadling et al., 2008)
				3/21 (14%) (Spendlove et al., 2004)
				23/78 (29%) (Griewank, Westekemper, et al., 2013)
				2/5 (40%) (Goldenberg-Cohen et al., 2005)
	14/28 (50%) (Goldenberg-Cohen et al., 2005)			10/39 (26%) (Cao et al., 2017)
	13-23 (56%) (Francis et al., 2018)	0/11 (0%) (Goldenberg-Cohen et al., 2005)	0/4 (0%) (Goldenberg-Cohen et al., 2005)	39/111 (35%) (Larsen et al., 2016)
	7/37 (19%) (Cao et al., 2017)	0/17 (0%) (Cao et al., 2017)	0/13 (0%) (Cao et al., 2017)	4/53 (8%) (Sheng et al., 2015)
	9/12 (75%) (Larsen et al., 2016)		2/8 (25%) (Larsen et al., 2016)	31/101 (31%) (Lally et al., 2022)
	15/35 (43%) (El Zaoui et al., 2019)			16/47 (34%) (Gardrat et al., 2021)
				13/28 (46%) (van Poppelen et al., 2021)
NRAS				4/14 (29%) (Cisarova et al., 2020)
				23/78 (29%) (van Ipenburg et al., 2021)
				11/31 (35%) (El Zaoui et al., 2019)
				0/11 (0%) (Beadling et al., 2008)
	9/23 (39%) (Francis et al., 2018)	NA	NA	14/78 (18%) (Griewank, Westekemper, et al., 2013)
				25/95 (26%) (Lally et al., 2022)
KIT				5/47 (11%) (Gardrat et al., 2021)
				6/28 (21%) (van Poppelen et al., 2021)
				1/14 (7%) (Cisarova et al., 2020)
	0/5 (0%) (Alessandrini et al., 2013)	NA	1/3 (33%) (Alessandrini et al., 2013)	1/13 (8%) (Beadling et al., 2008)
				0/42 (0%) (Griewank, Westekemper, et al., 2013)

					0/8 (0%) (Alessandrini et al., 2013)
					6/53 (11%) (Sheng et al., 2015)
					2/47 (4%) (Gardrat et al., 2021)
					2/28 (7%) (van Poppelen et al., 2021)
					12/38 (32%) (Griewank, Murali, et al., 2013)
					16/39 (41%) (Koopmans et al., 2014)
					20/47 (43%) (van Ipenburg et al., 2021)
TERT	0/56 (0%) (Koopmans et al., 2014)	0/14 (0%) (Koopmans et al., 2014)	2/25 (8%) (Koopmans et al., 2014)		15/24 (54%) (van Poppelen et al., 2021)
					9/14 (64%) (Cisarova et al., 2020)
					34/78 (43%) (van Ipenburg et al., 2021)
					21/63 (33%) (Scholz et al., 2018)
NF1	NA	NA	NA		29/74 (39%) (Lally et al., 2022)
					7/14 (50%) (Cisarova et al., 2020)

Other rarer mutations have been reported in the genes: CTNNB1, ACSS3, RET, TP53, CKIT, TET2, CDKN2A, MAPK2, RAC1, MET, SF3B1, GNAQ and GNA11 [12,13,16,58–60].

Transcriptomic studies in Co-M focussing on the immune tumour microenvironment have demonstrated high PDL1-expression, and a transcriptomic subtype enriched with immune genes (immune cell-types) [12,20,21].

3. Precursor lesions (C-MIL)

Approximately 70% of Co-M arise from conjunctival melanocytic intraepithelial lesions (C-MIL), also known as conjunctival melanocytic intraepithelial neoplasia (C-MIN) or primary acquired melanosis (PAM), whilst a smaller proportion develop from pre-existing nevi or de novo [3,4,61,62]. C-MIL, a precursor or preinvasive disease to Co-M, encompass a spectrum of morphological changes ranging from melanocytic hyperplasia through degrees of melanocytic atypia to melanoma in situ [63].

Both C-MIL and Co-M most frequently develop in the interpalpebral zone suggesting an association with ultraviolet (UV) radiation [45] with a number of studies revealing UV signatures (C > T transitions) [12,64–66]. However, both can also develop in non-sun-exposed sites but the mechanisms for this are unknown [18].

C-MIL shares the same demographics but may occasionally occur in teenagers and young adults. In a North American analysis of 311 eyes with C-MIL, 96% of the cases were in White individuals and 4% in Blacks, Hispanics, or Asians, with a patient age range of 15–90 years (mean: 56 years) [23,67].

4. Clinical presentation and assessment

Co-M is often unilateral and can affect any part of the conjunctiva but commonly presents on the bulbar surface, near the limbus (Figure 1). Invasion of the cornea, eyelid, sclera or orbit may occur in advanced tumours [4]. The lesions vary in size, shape and colour. Nodular masses may be well circumscribed, while flat lesions may have irregular, ill-defined margins, especially where there is adjacent C-MIL. Colour may range from amelanotic (pinkish) to various shades of brown or even black and be patchy or mixed within the one lesion [68]. Patients may present on noticing a mass with/without pigmentation on their eye but can also have significant visual morbidities, such as: irritation/burning with redness and reflex tearing, dry eye, pain, vision disturbance, double vision or vision loss [4,69,70].

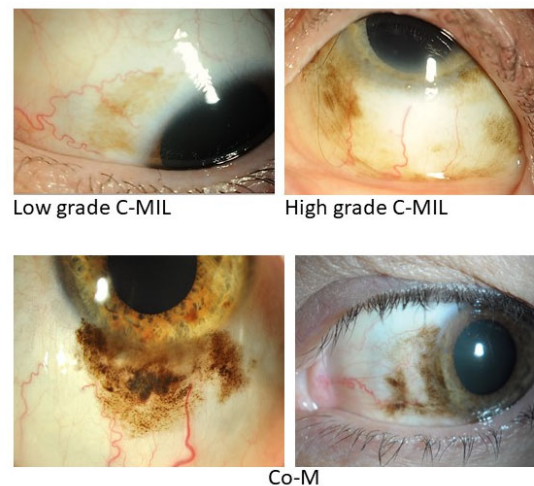


Figure 1. anterior segment photographs of C-MIL and Co-M.

Differential diagnoses of Co-M, include benign conjunctival nevi, extraocular extension of uveal melanoma or melanocytoma (black lesions), pigmented conjunctival squamous cell carcinoma, or very rarely metastasis of cutaneous melanoma. In amelanotic lesions, differentials also include conjunctival squamous intraepithelial neoplasia, squamous cell carcinoma or lymphoma [70]. Lack of cysts (often observed in conjunctival nevi), tumour haemorrhage, large/deep tumour, tortuous feeder vessels, adherence to underlying and invasion into surrounding structures, and multifocal lesions favour melanoma over conjunctival nevus [71].

C-MIL are unilateral but most often multifocal, can involve any part of the conjunctiva (bulbar, limbal, forniceal, and palpebral, in order of decreasing frequency) (Figure 1), and may extend to the caruncle, plica and cornea. They appear as mobile, flat, irregular brown pigmented conjunctival discolorations, which may change over time [14,22,23,39,40,67]. Rarely, C-MIL can be amelanotic, making it diagnostically challenging [22,23]. Differential diagnoses of C-MIL include: benign epithelial melanosis, oculodermal melanocytosis, conjunctival nevi, Co-M, pigmented conjunctival squamous intraepithelial neoplasia [72], Addison's disease [73], post-inflammatory hyperpigmentation, and conjunctival tattooing [74].

Imaging of all conjunctival melanocytic lesions involves regular anterior segment photo-documentation (including with eversion of eyelids), slit lamp biomicroscopy, and possibly ultrasound (to estimate tumour thickness or look for orbital involvement). There are recent developments in anterior segment optical coherence tomography [75,76] and in vivo reflectance confocal microscopy [77]. Where Co-M has locally extended into the eyelid and particularly if there is any suspicion of orbital or nasolacrimal invasion, MRI has a critical role in the assessment; diffusion and perfusion-weighted imaging can help in differentiating Co-M from other eyelid masses [78].

5. Histomorphological features

Co-M shares similar histomorphological features to those of cutaneous or other mucosal invasive melanoma [79]. The intraepithelial (radial) component can be nested, pagetoid, lentiginous, or rarely absent. It can also extend beyond the invasive component and involve adjacent structures. The invasive stromal (vertical) component can comprise nests or sheets of atypical melanocytes with cytology ranging from small naevoid-type cells to highly atypical pleomorphic melanocytes with spindle or epithelioid type. Nuclei can be hyperchromatic with inconspicuous nucleoli or vesicular with prominent eosinophilic nucleoli (Figure 2). Ulceration, mitotic activity, angiotropism, satellites in transit metastases, and neurotropism may be seen. A pre-existing nevus also may be present. Melanophages and variable lymphocytic infiltrate are also often observed. Increased mitoses (> 5.5 mitoses/mm²) have been associated with nodal metastasis; ulceration and greater tumour thickness have been associated with increased mortality similar to skin melanoma [80,81].

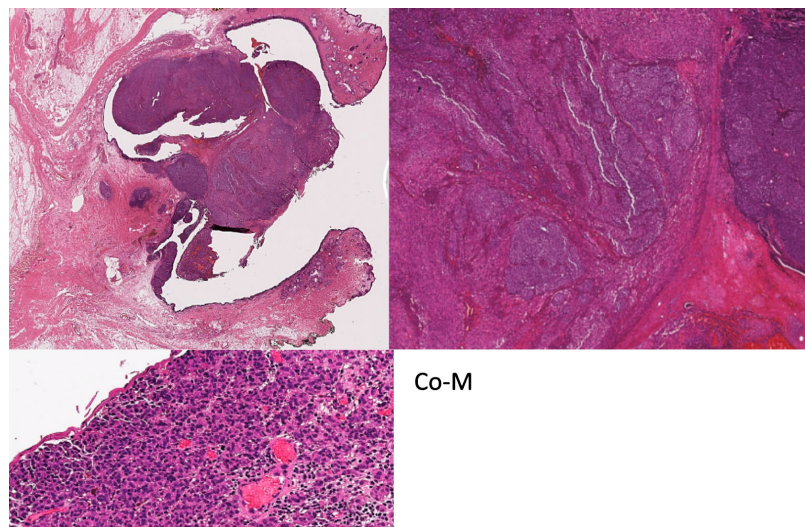


Figure 2. Histomorphological H&E micrographs of Co-M.

The key histomorphological features in C-MIL are increased cellularity/hyperplasia of intraepithelial conjunctival melanocytes with increasing cytological atypia, but the basement membrane remains intact [79,82,83]. The spectrum of cytological features ranges from small melanocytes with nuclear hyperchromasia and scant cytoplasm to severely atypical large pleomorphic epithelioid cells with ample cytoplasm and prominent eosinophilic nucleoli. The range of atypical architectural patterns include linear hyperplasia of basal melanocytes to confluent lentiginous spread, intraepithelial nests, pagetoid growth, and full thickness epithelial involvement by atypical melanocytes, i.e., melanoma in situ. Nests, pagetoid spread and confluent growth extend upward from the basal epithelium, displacing squamous and/or goblet cells but there should be no evidence of invasive growth [63,79,82,83]. Epithelioid cell morphology with cytological atypia, nesting and pagetoid spread are associated with an increased risk of recurrence and progression to Co-M [23,79,82,84,85].

Terminologies more commonly used to classify these lesions include PAM with atypia and C-MIN, and the most recently validated C-MIL [83,86]. Various grading or scoring systems have been used for C-MIL [22,73,82,83,85,87–89]. The grading of the cytological atypia in PAM (mild, moderate, or severe), which was similar to those used in the skin and other mucosal sites [82,84], suffered from poor reproducibility between pathologists. The C-MIN scoring system was based on architectural features (i.e., horizontal, and vertical spread) and cytological atypia but can be time-consuming and complex [87].

In 2018, the 4th 'WHO Classification of Eye Tumours' proposed the C-MIL classification, simplifying the grading of these lesions and capturing their risk of disease progression to invasive

melanoma [90]. This comprised: 1) low-grade C-MIL (corresponding to PAM with or without mild atypia or C-MIN scores 1-2; 2) high-grade C-MIL (PAM with moderate to severe atypia or C-MIN 3-5); and 3) conjunctival melanoma in-situ (PAM with severe atypia involving >75% of the epithelium or a C-MIN score >5). The system was validated in 2021 and was found that all 3 classification systems (C-MIL, C-MIN and PAM) had comparable accuracy in their ability to identify lesions with potential for recurrence [83]. In 2022, the editorial panel of the 5th edition decided to revise the classification scheme because the low-grade C-MIL in the 4th edition incorporated both non-neoplastic and neoplastic melanocytic proliferations. This led to the current system as summarised in Table 2 [63]. This was validated by a large international collaborative study and found to have substantial interobserver agreement, good reproducibility, be predictive of recurrence and invasive disease, and importantly, inform clinical treatment thresholds [86]. Photomicrographs demonstrating the C-MIL scoring grades are presented in Figure 3 [86].

Table 2. 2022 WHO classification of conjunctival melanocytic intraepithelial lesions (C-MIL) [63].

WHO	Acceptable alternative terminology	Increased cellularity	Histologic features	Risk of progression to invasive melanoma
Not applicable	Benign melanosis C-MIN (grades (0-1) PAM without atypia	No/minimal	Conjunctival hypermelanosis (increased pigment in epithelial cells without melanocytic hyperplasia or atypia). Slight or focal melanocytic hyperplasia without atypia (parabasal melanocytes with condensed round nuclei, smaller than basal epithelial cell, inconspicuous nucleoli, and inconspicuous cytoplasm) may be seen.	None
Low-grade C-MIL	PAM with mild atypia C-MIN (grades 2-4)	Yes	Predominantly basilar melanocytic proliferation with low-grade atypia (dendritic or small to moderate size polyhedral, usually non-epithelioid melanocytes with round to irregular nuclear contours, often nuclear hyperchromasia, inconspicuous nucleoli, and inconspicuous or scant cytoplasm).	Lower
High-grade C-MIL	PAM with moderate to severe atypia C-MIN (grade 5-10)	Yes	More confluent basilar and significant non-basilar proliferation of melanocytes with high-grade atypia (moderate to severe), evidence of intraepithelial nested and/or pagetoid growth, and epithelioid cell cytomorphology.	Higher
High-grade C-MIL	Melanoma in situ	Yes	The term melanoma in situ may be used for (1) the most atypical high-grade C-MILs involving close to full thickness of the epithelium, (2) histologically obvious melanomas without documented evidence of subepithelial invasion.	Highest

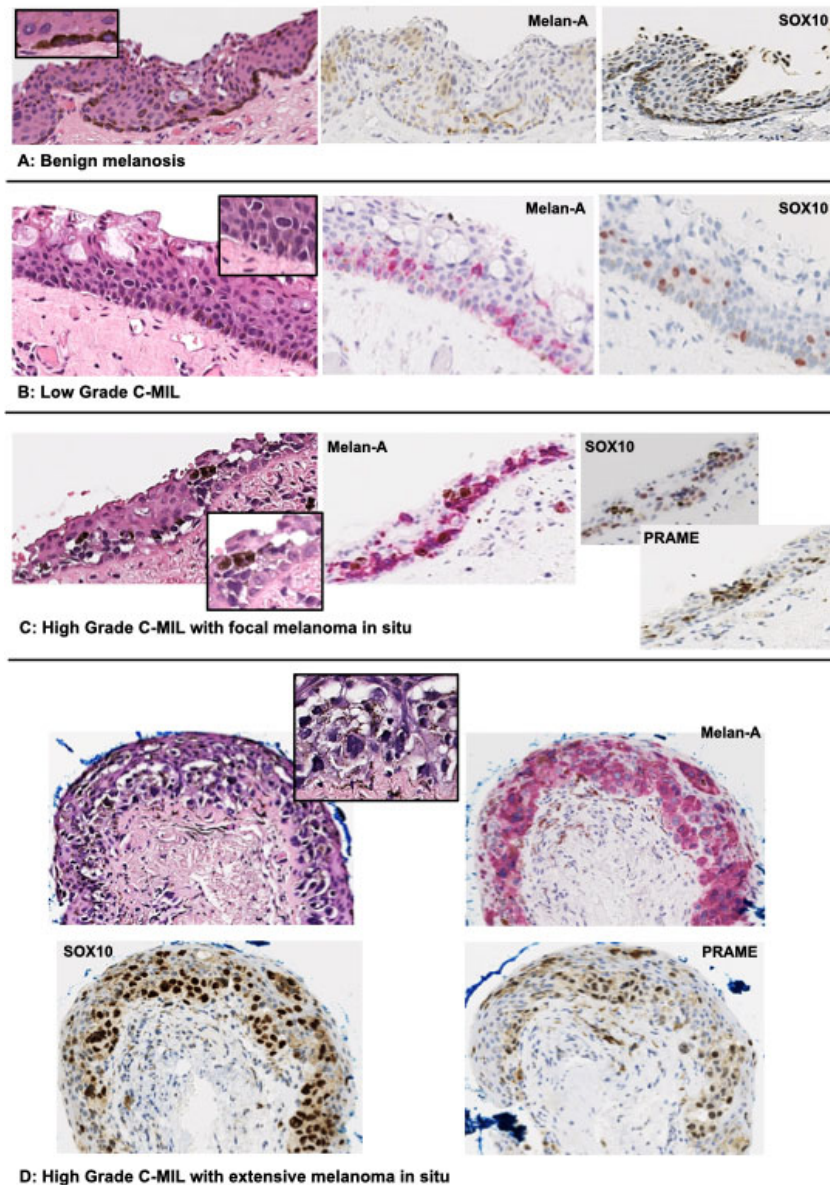


Figure 3. Photomicrographs representing the C-MIL grading system [86].

All conjunctival melanocytic lesions immunohistochemically show MelanA (MART1), S100, SOX10, HMB45 (should only be present in superficial areas of nevi) and MITF (Melanocyte Inducing Transcription Factor). Nuclear expression of PRAME (Preferentially expressed Antigen in Melanoma), cyclin D1 positive and loss of p16 on immunohistochemistry can also be helpful in distinguishing Co-M from nevi or low grade C-MIL (both PRAME and cyclin D1 negative, p16 positive) [53,86,91–94]. PD-L1 may be expressed [95].

Melanoma in-situ and Co-M are staged by the AJCC/UICC TNM 8th edition system which has been validated for development of metastasis and survival [96–98].

6. Treatment and prognosis

Approximately 70% of all Co-M arises from high grade C-MIL [73]; hence there is an absolute clinical need to know when to treat patients [22,23,86]. There is no standard-of-care for C-MIL or Co-M; consequently, management varies considerably between ophthalmic and specialised ocular oncology centres. This includes: surgical excision (wide local) +/- amniotic membrane allograft and +/- adjuvant cryotherapy, topical chemotherapy (mitomycin C, 5-fluorouracil or interferon alpha-2b), radiotherapy (brachytherapy, proton beam or photon external beam) or radical orbital exenteration for advanced cases with local tissue invasion [4,22,23,32,70].

Reported usefulness of sentinel lymph node biopsy (SLNB) is variable (in terms of clinical management and sensitivity of pickup) but shown to be effective for Co-M >2mm thickness and/or >10mm in diameter [99].

The postoperative complications rate (vision loss, scarring, limbal stem cell failure, ulceration/non-healing defects, etc) and risk of tumour recurrence are very high (33-61%), warranting close life-long follow-up [4,28–31,70]. Lymph node metastases are common (~25-52%; preauricular, parotid, submandibular and/or cervical nodes, depending on Co-M location) but may also involve the liver, lungs and brain (11-42%). Poor prognostic indicators/risk factors for nodal and systemic metastases, include a non-epibulbar locations, ulceration and increased tumour thickness [32,33,61,62,80,81]. The 5-year and 10-year disease-specific mortality rate is ~14-27% and 25-35%, respectively [4,30,32,33,61,62,70,100]. Similarly to the risk of metastases, tumour-related death has been associated with de novo origin, non-bulbar conjunctival location, nodular growth, multifocal lesions, and sentinel lymph node positivity [4,30,43,80,101].

The use of genetics for prognostication in Co-M is currently limited. However, as mentioned above, Co-M has genetic alterations similar to those of cutaneous melanoma, and advances in characterising Co-M genetics are offering insight into potential targeted therapies that are already in use for the treatment of cutaneous melanoma. Data on Co-M (anti-BRAF; anti-MEK; anti-PD-L1) with targeted/immunotherapies have shown promising results but are limited, with only those from small case series or single case studies in patients with inoperable disease or as first-line therapy prior surgery in advanced cases [18,34,35,38,102]. A summary of targeted therapies and immune checkpoint inhibitors are presented in Tables 3 [103–106] and 4 [107–109], respectively. A Phase 2 clinical trial using a combination of axitinib and nivolumab in untreated advanced or metastatic mucosal melanoma (head & neck and conjunctival; NCT05384496) is underway.

Table 3. Reported cases of targeted therapy in Co-M.

Study	Patient	Co-M	Primary treatment	Agent used	Dosage	Outcome	Adverse reactions
Indicated for primary CoM							
(Pahlitzsch, 2014)	80y, Female	BRAF mutation	Exenteration (rejected)	Vemurafenib		Successful tumour response Tumour decreased in size	8kg weight loss Nausea vomiting, headaches
Indicated for metastatic disease							
(Weber et al., 2013)	45y, Male	Metastatic Co-M (nodal, subcutaneous, pulmonary, osseous) BRAF mutation v600e	Resection	Vemurafenib	960mg twice daily	Improvement in pain and subjective tumour regression after 1 month	Disease progression 2 months into treatment. Enlarged paraspinal mass.

(Malek a et al., 2016)	53y, Female	Metastatic Co-M (orbit, parotid gland, lung, brain) BRAF mutation v600e	Excision Cryotherapy Mitomycin eye drops Enucleation	Vemurafenib	960mg twice daily	Initially good response and reduction of mets, after 4 months reappearance of mets and death,	Skin rash (dose reduced to 720mg twice daily)
(Rossi et al., 2019)	70y, Male	Metastatic Co-M (parotid gland and lymph node) BRAF mutation v600e	Excisional biopsy	Dabrafenib Trametinib	Dabrafenib (150mg twice daily) Trametinib (2mg daily)	Reduction of lymph node metastasis activity	Fever
(Pinto Torres et al., 2017)	59y, Female	Metastatic Co-M (Oropharyngeal wall) BRAF mutation v600	Excision	Vemurafenib	960mg twice daily	Full symptomatic recovery after 1 month	Arthralgia, diarrhoea, skin rash (dose was reduced to 480mg twice daily)

Table 4. Reported cases of immune checkpoint inhibitor therapy in Co-M.

Study	Patient	Co-M	Primary treatment	Agent used	Dosage	Outcome	Adverse reactons
Indicated for primary CoM							
(Finger & Pavlick, 2019)	94y, Female	Bulbar to eyelid	None (rejected exenteratio n)	First – Pembrolizumab Second – Pembrolizumab and ipilimumab	Pembroliz umab – 200mg Ipilimuma b – 1mg/kg	Progression	None reported
(Finger & Pavlick, 2019)	76y, Male	Recurrence. Cornea to eyelid	Local treatments and topical interferon-alpha chemotherapy	First – ipilimumab Second – Pembrolizumab Third – Pembrolizumab and IFN-alpha	Pembroliz umab – 2mg/kg	Ipilimumab – no response Pembrolizu mab – minimal response then complete with IFN-alpha	Ipilimumab - Adrenal insufficiency Pembrolizuma b – Dermatitis
(Finger & Pavlick, 2019)	84y, Female	Recurrence. Cornea to eyelid	Excision Cryotherap y Topical mitomycin Eye plaque brachythera py	First – Pembrolizumab Second – Pembrolizumab and ipilimumab Third – Pembrolizumab and ipilimumab and IFN-alpha	Pembroliz umab – 200mg Ipilimuma b – 1mg/kg IFN-alpha – 3 million units per eyelid	Pembrolizu mab – minimal success Pembrolizu mab and ipilimumab – progression	None reported

(Hong et al., 2021)	53y, Female	Bulbar to tarsal	None	Pembrolizumab	200mg	Complete reduction of pigment and disease free 12 months of follow up	Cutaneous pruritus
Indicated for metastatic disease							
(Pinto Torres et al., 2017)	51y, Male	Co-M recurrence with metastasis (lymph) No BRAF mutation	Excision Lymphadenectomy	Pembrolizumab	2mg/kg every 3 weeks	Complete resolution of subcutaneous lesions	None noted, patient on complete remission
(Sagiv et al., 2018)	68y, Female	Co-M recurrence Metastasis – lung BRAF v600e mutation	Resection Topical mitomycin C Exenteration, sentinel lymph node biopsy	First – Pembrolizumab Second – Ipilimumab and dacarbazine	Pembrolizumab 2mg/kg every 3 weeks Ipilimumab – 3mg/kg Dacarbazine – 800-1000mg/m ²	Pembrolizumab – stable at 6 months	Ipilimumab and dacarbazine - hepatotoxicity
(Sagiv et al., 2018)	58y, Female	Co-M recurrence to orbit Metastasis – lung and liver	Multiple resections Orbital exenteration	nivolumab	3mg/kg every 2 weeks	Complete resolution or orbit and metastasis lesions	Elevated liver enzymes
(Sagiv et al., 2018)	28y, Female	Co-M recurrence Metastasis – breast, lung and bone	Excision Cryotherapy Topical mitomycin C	nivolumab	3mg/kg every 2 weeks	Complete resolution	None reported
(Sagiv et al., 2018)	47y, Female	Co-M recurrence Metastasis – lung	Excision Cryotherapy Radiotherapy Topical interferon Mitomycin C	nivolumab	3mg/kg every 2 weeks	Resolution of lung metastasis and free from disease 7 months after nivolumab	Diarrhoea
(Sagiv et al., 2018)	74y, Male	Co-M recurrence Metastasis – lung	Multiple excision	nivolumab	3mg/kg every 2 weeks	Decrease in tumour size Disease free 1 month after nivolumab	Colitis
(Chaves et al., 2018)	72y, Male	Recurrent Co-M Metastasis – Lung	Debulking and sentinel lymph node biopsy Radioactive iodine 125	Ipilimumab	3mg/kg every 3 weeks	Satisfactory response to treatment and excellent local tumour control	Mild fatigue

(Finger & Pavlick, 2019)	72y, Female	Epibulbar BRAF v600k Metastasis – liver, lung, bone, skin, lymph node	Local excision and topical chemotherapy	Ipilimumab and nivolumab	Ipilimumab – 3mg/kg Nivolumab – 1mg/kg	Resolution of subcutaneous nodules Reduction of systemic tumour burden	Hepatotoxicity Colitis
(Finger & Pavlick, 2019)	76y, Female	NRAS mutation Metastasis – lymph, skin	Excision Cryotherapy Topical mitomycin chemotherapy	First – ipilimumab Second – ipilimumab Third - Pembrolizumab	Ipilimumab – 3mg/kg Pembrolizumab – 200mg	Ipilimumab – new skin metastases and lymph metastases	None reported
(Kiyohara et al., 2020)	71y, Male	Co-M recurrence BRAF v600e Metastasis – bone and liver	Excision Cryotherapy Vemurafenib	Nivolumab	-	Died 24 months after combined therapy	None reported
(Hong et al., 2021)	66y, Male	Fornix and orbit Metastasis – lung and liver	None	Ipilimumab and nivolumab	No dose mentioned	Resolution of lesion and good response to mets	Pituitary failure

7. Conclusions and future directions

Co-M is a rare, aggressive, invasive eye and eyelid cancer with increasing global incidence. Given the rarity of Co-M, international collaboration is pivotal to obtain sufficient numbers in order to progress translational research and enlist Co-M patients into clinical trials. The recent developments in cancer genetics and immunology present exciting new frontiers in better understanding of Co-M pathogenesis, and importantly provide new targets for therapy. Insight into the molecular drivers for Co-M development and its integration with clinical and histomorphological evaluation will allow earlier diagnosis, improve risk stratification and prognostication, and identify patients for specific therapies (i.e. ‘personalised/precision medicine’). This will further enable the development of clear management guidelines and enrolment into targeted therapies earlier than current practice, facilitating improved outcomes in this rare disease.

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