Many patients with conjunctival melanoma experience suboptimal outcomes because of iatrogenic tumor seeding, inadequate local tumor control, and surgical morbidity.

Management of Primary Acquired Melanosis, Nevus, and Conjunctival Melanoma

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Background: The management of conjunctival melanoma is difficult because of the rarity of the disease, confusing terminology, high rates of local tumor recurrence, controversies regarding treatment, a poor evidence base, unreliable prognostication, and significant mortality rates.

Methods: The medical literature was reviewed, focusing on treatment and management options for conjunctival melanoma. Recent trends and developments were summarized with respect to terminology, local treatment, histology, genetic analysis, prognostication, and systemic treatment, highlighting the scope for research and possible improvements in patient care.

Results: Histopathological diagnostic terminology for primary acquired melanosis is being superseded by more explicit terminology, thus differentiating hypermelanosis from conjunctival melanocytic intraepithelial neoplasia. Topical chemotherapy and increased use of adjunctive radiotherapy have helped improve rates of local tumor control. Use of exenteration has become rare. Regional and systemic metastases are common in patients with nonbulbar conjunctival melanoma, although long-term survivors with metastases are growing in number. Prognostication is mainly based on tumor size and location, but histological and genetic data into multivariate analyses will soon be incorporated. The role of sentinel lymph-node biopsy continues to be controversial. Chemotherapy for metastatic disease is being superseded by targeted therapy based on genetic abnormalities such as BRAF mutations.

Conclusions: The management of conjunctival melanoma requires expert care from an experienced, multidisciplinary team. The goal of therapy is to provide good local tumor control with minimal morbidity, high-quality pathology, and adequate psychological support. Maximizing patient enrollment in multicenter clinical trials is likely to strengthen evidence-based decision-making.

Introduction
Conjunctival melanoma is a rare but potentially sight- and life-threatening malignancy of the eye. It arises from melanocytes of the basal layer of the conjunctival epithelium and comprises approximately 2% to 7% of ocular melanomas. The incidence is approximately 0.24 to 0.8 cases per 1 million and is increasing. Risk factors for conjunctival melanoma are not well understood because of the rarity of the disease and lack of large population-based studies. The disease is most common in whites and rare in Asian/Pacific Islanders. Most studies have not shown any sex predilection. Conjunctival melanoma has a
strong association with primary acquired melanosis (PAM) and conjunctival nevi. Conjunctival melanoma tends to locally recur, seed to distant parts of the conjunctiva, and systemically metastasize to regional lymph nodes. Once metastatic disease has occurred, outcomes are often fatal.

**Classification of Conjunctival Pigmented Lesions**

Melanocytic lesions of the conjunctiva are generally classified as PAM, nevus, and melanoma (Fig 1).

The term *PAM* tends to be both clinically and histologically used. Although this term is adequate for clinical findings, it is not ideal for histological diagnosis because it encompasses a wide range of conditions, from benign to malignant, that include complexion melanosis and PAM with and without atypia. Furthermore, PAM with atypia tends to be categorized as mild, moderate, or severe, and is often inconsistently used. To improve the rate of precision in the reporting of histological findings, Damato and Coupland recommend distinguishing between hypermelanosis and conjunctival melanocytic intraepithelial neoplasia. In their classification, hypermelanosis refers to the overproduction of melanin from a normal population of melanocytes, as occurs with complexion/racial melanosis. To make classification more consistent, Damato and Coupland have created a system for scoring the grade of malignancy from 0 to 10 according to pattern of melanocytic proliferation, extent of vertical spread, and degree of cellular atypia (Table).

Conjunctival melanocytic intraepithelial neoplasmia with a score of 0 would correspond with PAM without atypia and would indicate an overpopulation of melanocytes showing no cellular atypia and confined to the basal layer of the epithelium. Higher scores correspond to PAM with atypia, indicating cellular atypia of melanocytes with invasion into the more superficial layers of the epithelium but without breaching the basement membrane of the epithelium. No consensus exists as to how severe PAM/conjunctival melanocytic intraepithelial neoplasia with atypia should be classified prior to being labeled as melanoma in situ. Damato and Coupland suggest designating any atypia with a score exceeding 5 as in situ, which corresponds to confluent proliferation of atypical melanocytes involving more than 50% of the thickness of the epithelium. This designation might improve communication between the pathologist and clinician, resulting in fewer delays of treatment due to vagaries in classification. Multicenter studies are needed to determine whether this 10-point scoring system improves objectivity and clinical care compared with simply categorizing disease as mild, moderate, and severe.

Conventionally, conjunctival melanoma implies invasion of the substantia propria, even if the word *invasive* is omitted. We believe that it would be safe practice to distinguish between melanoma in situ and

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Fig 1A–F. — Clinical features of pigmented conjunctival lesions. (A) Complexion melanosis appearing as diffuse conjunctival pigmentation in a pigmented individual. (B) Primary acquired melanosis manifesting as a discrete patch of conjunctival pigment. (C) Nevus shown as a slightly elevated pigmented lesion with intraepithelial cysts. (D) Invasive melanoma demonstrated as a pigmented nodule arising from a patch of conjunctival melanosis. (E) Invasive melanoma of the palpebral conjunctiva. (F) Invasive melanoma with locally disseminated disease, due to prior biopsy at an outside institution, without use of adjuvant therapy.
invasive melanoma when discussing pathology. In the presence of invasive melanoma, it can be difficult or impossible to histologically distinguish between primary conjunctival melanocytic intraepithelial neoplasia that caused invasive melanoma and pagetoid spread from the invasive tumor.

Damato and Coupland suggest that PAM is limited to clinical findings and that histological reports should distinguish between hypermelanosis and melanocytic intraepithelial neoplasia, numerically scoring the degree of malignancy instead of using vague terms such as mild, moderate, and severe.

Clinical Features
Melanoma in situ presents as 1 or more brown patches developing anywhere in the conjunctiva, almost always unilaterally, and becoming more extensive over time. Melanocytic proliferation can become amelanotic, especially after unsuccessful treatment.

Invasive conjunctival melanoma can be nodular, diffuse, or mixed; deeply pigmented, lightly pigmented, or amelanotic; unifocal or multifocal; and with or without adjacent melanosis. Amelanotic melanomas can be white, yellow, pink, or red in color. Feeder vessels are usually present. Hemorrhage does not keratinize. Most tumors are located in the bulbar conjunctiva, usually involving the limbus. Less commonly, tumors may present on the palpebral or fornical conjunctiva, plica semilunaris, or caruncle. Regional lymph nodes may be enlarged if regional metastasis has occurred.

Differential Diagnosis
Primary acquired melanosis requires incisional biopsy to distinguish diffuse invasive melanoma and melanoma in situ from hypermelanosis and conjunctival melanocytic intraepithelial neoplasia without atypia (ie, PAM without atypia). Congenital ocular melanocytosis is slate-grey in color rather than brown and involves the sclera alone; the overlying conjunctiva is transparent. Conjunctival nevi tend to have multiple cysts and are not associated with feeder vessels, except when occurring in children. Squamous cell carcinoma is usually amelanotic but can be deeply pigmented, especially in dark-skinned individuals. It usually presents as frosty keratinization, which does not occur with melanoma. Typically, lymphoma has a salmon-pink color, is located in the plica and fornice, and is bilateral. Rare mimicking lesions can include pinguecula, pterygium, pyogenic granuloma, deposition of pigmented foreign material, extraocular spread of uveal melanoma, metastasis from cutaneous melanoma, staphyloma, subconjunctival hematoma, foreign body, and hematic cyst.

Clinical Examination
Examination of the entire conjunctiva must include the superior fornix and superior palpebral regions, either after double eversion of the upper eyelid with a Desmarres retractor or by pinching and lifting the upper lid away from the bulbar conjunctiva while performing inspection with a binocular indirect ophthalmoscope and a 20-D lens. The preauricular, postauricular parotid, submandibular, and cervical lymph nodes are routinely palpated.

Imaging
Color drawings are valuable for defining tumor size and extent; Fig 2 can be used as a template for this purpose. In addition, if performed correctly, color photography with adequate retraction of the eyelids is useful for documenting surface features and tumor margins.

Table. — Coupland–Damato Scoring System for Conjunctival Melanocytic Intraepithelial Neoplasia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanocytic pattern</td>
<td>No melanocytic neoplasia (+ hypermelanosis)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Basal/lentiginous proliferation <em>or</em> Pagetoid spread (+ basal/lentiginous) <em>or</em> Nonconfluent nests (+ basal/lentiginous pagetoid) <em>or</em> Confluent nests (+ basal/lentiginous pagetoid)</td>
<td>1</td>
</tr>
<tr>
<td>Vertical spread of melanocytes with atypia</td>
<td>Basal layer of epithelium</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 50% epithelial thickness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>50%–90% epithelial thickness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total replacement of epithelium</td>
<td>3</td>
</tr>
<tr>
<td>Cellular atypia</td>
<td>Nuclei &lt; basal squamous cells</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nuclei ≥ basal squamous cells</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cytoplasm &lt; basal squamous cells</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cytoplasm ≥ basal squamous cells</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nucleolus and mitoses absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nucleolus + mitoses present</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>(Must be ≤ 10 points)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of specimen invaded by most severe disease, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Changes extend to or near lateral resection edge(s)</td>
<td>Yes/No</td>
</tr>
<tr>
<td></td>
<td>Invasive melanoma (if yes, report elsewhere)</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

neoplasia without atypia appears as normal-thickness epithelium, with strong hyper-reflectivity of the basal epithelium, correlating with the basal layer of melanocytes seen on histopathology. Nevi are hyper-reflective, well circumscribed, and often have visible cysts, with appearances varying according to whether the lesion is junctional, compound, or subepithelial. Invasive melanoma reveals subepithelial disease that casts a significant shadow (Fig 3). Ultrasonographic biomicroscopy using transducers between 50 and 100 MHz can measure the thickness of conjunctival melanomas with reasonable accuracy and may identify tumors greater than 2 mm in thickness so that sentinel lymph-node biopsy can be planned before tumor excision. High-frequency ultrasonography can be useful for detecting or excluding suspected underlying uveal melanoma.

**Diagnosis**

**Histology**

Histology by a trained pathologist is required to differentiate between hypermelanosis, conjunctival melanocytic intraepithelial neoplasia, in situ melanoma, invasive melanoma, and other pathology. Bleaching of specimens is often required to examine cell morphology. Features of atypical melanocytes include nuclear pleomorphism, prominent nucleoli, increased eosinophilic cytoplasm, and mitotic figures.

Hypermelanosis is characterized by increased melanin granules within normal melanocytes in the basal epithelium. Conjunctival melanocytic intraepithelial neoplasia with a score of 0 consists of an increased number of melanocytes without atypical features (Fig 4A). Conjunctival melanocytic intraepithelial neoplasia with higher scores is identified by intraepithelial growth of atypical melanocytes, extending up to full thickness, but with no invasion through to the epithelial basement membrane (Fig 4B). Invasive melanoma is defined by atypical melanocytes that have invaded the basement membrane into the substantia propria (Fig 4C).

Histological assessment has been improved due to the development of immunohistochemistry. Markers for melanocytes include S100, human melanoma black 45, SRY-box containing gene 10, and Melan-A. A red chromogen is useful in the presence of a heavily pigmented lesion.
Biopsy

Incisional biopsy of nodular melanoma can cause tumor seeding, so it should be performed for PAM alone; otherwise, excisional biopsy is preferred when possible. The specimen should be placed on a stiff card or filter paper to prevent scrolling so that oblique histological sections are avoided. Care must be taken to avoid crush artifact. Testing for \( \text{BRAF} \) mutations should be considered at this stage if concern exists for metastatic disease potentially treatable with \( v-raf \) murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors. When a patient is referred to an oncology center after biopsy, we routinely arrange for our ophthalmic pathologist to review the histology results.

Treatment

Surgical Excision

The conventional approach to treatment is to excise nodular conjunctival melanomas with wide safety margins and lamellar scleral dissection, to ensure deep and lateral clearance, and to administer adjunctive cryotherapy as a precaution. Such extensive surgery often requires amniotic membrane grafting, which can result in significant morbidity (eg, corneal scarring, scleral translucency). Furthermore, significant rates of local tumor recurrence have been reported, sometimes exceeding 30%. Growing circumstantial evidence suggests that such local recurrence is associated with higher rates of mortality.

For at least 15 years, the approach was to excise the tumor with minimal surgical clearance, perform no lamellar scleral excision, and provide no adjunctive cryotherapy, instead administering adjunctive radiotherapy for all cases with invasive melanoma, irrespective of histological evidence of clearance. In addition, adjunctive topical chemotherapy is warranted if adjacent intraepithelial neoplasia is present, whether this consists of primary disease or secondary pagetoid spread.

Many patients are referred to an oncology center after undergoing incisional biopsy or excision by surgeons not following the “no touch” technique or who may not understand the importance of using fresh instruments for closure to avoid seeding. After witnessing recurrences in distant parts of the conjunctiva in such cases, Damato and Coupland routinely administer adjunctive topical chemotherapy to all such patients irrespective of histological findings. Although data are insufficient for statistical evaluation of this approach, clinical impressions have been positive.

Primary Exenteration

Primary exenteration has been abandoned as a primary treatment for PAM. Such extensive surgery is now performed for advanced invasive melanoma alone.

Adjuvant Therapy

Cryotherapy: Historically, cryotherapy was the only treatment for PAM/conjunctival melanocytic intraepithelial neoplasia with atypia; in modern times, its use is advocated by some as adjunctive therapy following local excision. It is delivered using the double or triple freeze-thaw technique. Jakobiec et al recommend using a liquid nitrogen probe and a subconjunctival thermocouple to ensure that a temperature of \(-20^\circ \text{C}\) is achieved; however, Damato and Coupland reported an unacceptable tumor recurrence rate in addition to complications such as uveitis, hyptonony, macular edema, and squamous metaplasia of the conjunctiva. This treatment has largely been superseded by topical chemotherapy. We now perform cryotherapy for residual or recurrent intraepithelial disease alone after at least 2 courses of topical chemotherapy.

Topical Chemotherapy: This type of treatment is administered using mitomycin C (MMC), because other agents such as fluorouracil are less effective. The standard protocol is to prescribe drops 4 times per day for 2 weeks, repeating the treatment after a 2-week rest period. We prefer a 1-week course of topical chemotherapy, repeated every 4 weeks for 4 cycles, because doing so causes less pain and inflammation as well.
as improved patient compliance. Topical steroids are helpful in reducing the inflammation, and our preference is to use 0.1% fluorometholone because it does not penetrate the globe. No consensus exists regarding the ideal dose of MMC. We prescribe 0.03% MMC because we found that lower concentrations were associated with local treatment failure, whereas higher doses caused limbal stem cell failure in select patients. Some authors advocate punctual occlusion during topical chemotherapy; however, we do not favor this practice, especially with patients who have tumor recurrence in the nasolacrimal system. When administering topical chemotherapy, the patient must be provided with disposable gloves, petroleum jelly to protect the eyelid skin, a disposal container (to be returned to the hospital with all soiled materials), and detailed oral and written instructions on the storage and administration of the MMC drops.

**Radiotherapy:** Radiotherapy can consist of brachytherapy, which uses isotopes such as strontium, ruthenium, or iodine, or teletherapy, which uses photons or a proton beam (Fig 5). Adjunctive radiotherapy after local excision was reported by Collins in 1918 and later by Lederman in 1958 but it has since fell into disuse. Damato and Coupland reported high rates of local tumor control with adjunctive ruthenium plaque radiotherapy, delivering a dose of 100 Gy to a depth of 1 mm, which involves suturing the plaque over the target area and removing it after 1 day with topical anesthesia. They found this to be less labor intensive than strontium brachytherapy, which requires delivery for several days. Iodine plaques are more bulky, so they are more likely to be uncomfortable for the patient; however, radiotherapy can be tailored to each individual by adjusting the number and distribution of the iodine seeds. Such tailoring of the radiation dose is easier with proton beam radiotherapy, which does not require surgery but may be inconvenient for the patient because of increased travel time. Proton beam radiotherapy may be useful for lesions in the nonbulbar conjunctiva, which cannot easily be treated with brachytherapy. Damato has also achieved good results with radiotherapy alone in select patients with unresectable tumors.

**Topical Interferon Immunotherapy:** This type of treatment is a relatively recent addition to the therapeutic armamentarium. Although interferon α-2b is commonly used to treat ocular surface squamous neoplasia and conjunctival papillomas, data are limited on its use for conjunctival melanoma. No consensus exists regarding the most appropriate dosing regimen. Several case series have shown it to be effective for the treatment of conjunctival melanoma and conjunctival melanocytic intraepithelial neoplasia with good rates of tolerance by patients; however, further studies are required to examine its efficacy and safety data in patients with pigmented conjunctival lesions.

**Outcomes**

**Loss of Vision**

Loss of vision can occur as a result of keratitis following tumor excision, cryotherapy, or topical chemotherapy; hypotony and macular edema can occur following bulbar cryotherapy; and cataracts can occur following radiotherapy.

**Patient-Reported Outcomes**

Outcomes reported by patients such as grittiness, discharge, epiphora, and concerns about appearance are common, but, to our knowledge, they have not yet been analyzed in a published study.

**Local Recurrence**

The rate of local recurrence of PAM/conjunctival melanocytic intraepithelial neoplasia has been reported to be 27%. The reported rate of progression to invasive melanoma following treatment for PAM/conjunctival melanocytic intraepithelial neoplasia ranges from 13% to 46%. Recurrent invasive melanoma has been reported in 8% to 62% of study patients at 5 years and in approximately 38% to 52% of study patients at 10 years. Factors associated with lower rates of local recurrence include extent of initial disease, the “no touch” surgical technique, and adjunctive therapy (particularly radiotherapy). Rarely, tumor recurrence can intraocularly occur, particularly if the Bowman membrane has been surgically disrupted and if adjunctive radiotherapy has not been administered.

**Secondary Exenteration**

Secondary exenteration was previously reported in 13% of study patients. It has now become rare due to improved rates of local tumor control.
Metastatic Disease
Metastasis can be regional, systemic, or both. Regional metastases develop by lymphatic spread and involve the parotid, preauricular, postauricular, and submandibular nodes. Systemic metastases can occur by lymphatic or hematogenous spread. Approximately 20% to 30% of patients develop regional metastases; of these, 50% subsequently develop systemic metastatic disease. Conversely, up to 25% of patients develop systemic metastases alone without any clinical evidence of regional metastases. Treatment for metastatic disease is the same as for cutaneous melanoma and includes cytotoxic chemotherapy, immunotherapy, and molecularly targeted therapy.

Histological Predictors
Histological predictors of metastasis include tumor thickness exceeding 2 mm, surface ulceration, epithelioid cytormorphology, high mitotic count, and microsatellites, as well as vascular invasion or lymphatic invasion.

Genetic Predictors
Genetic predictors of metastasis have not been identified, although BRAF, CDKN1A, RUNX2, MLH1, TIMP2, MGMT, and ECHS1 have been reported. BRAF V600E mutation occurs in about 50% of cases of conjunctival melanomas. Approximately 50% of such melanomas respond to systemic BRAF inhibitors, so routine testing for this mutation occurs in some centers.

Further Studies
Diagnosis
In theory, hope exists for the external validation and refinement of the Damato–Coupland scoring system for conjunctival melanocytic intraepithelial neoplasia; however, in practice, the system is limited by the rarity of invasive melanoma in such cases, because most patients now receive treatment. High-resolution ocular coherence tomography is now available, so this imaging modality could be used to detect various grades of conjunctival melanocytic intraepithelial neoplasia, not only at presentation but also following topical chemotherapy. Such imaging could reduce the need for conjunctival biopsies.

Treatment
In view of the morbidity caused by topical MMC, we avoid such treatment in patients with conjunctival melanocytic intraepithelial neoplasia who have a score of 3 or below, instead preferring long-term surveillance for such cases. It would be useful to determine how many such patients develop more severe conjunctival melanocytic intraepithelial neoplasia, invasive melanoma, or both. With regard to invasive disease, future randomized trials should study extensive resection and cryotherapy compared with minimalist resection with radiotherapy and topical chemotherapy. Such studies should measure both patient-reported and clinical outcomes (ie, local tumor control, ocular conservation, vision, metastasis-free survival rates). Instruments for measuring patient-reported outcomes must be validated in the setting of conjunctival melanoma.

Prognostication
Survival estimates for patients with choroidal melanomas have been improved by mathematical methods that combine the AJCC staging system with histological...
grade of malignancy and genetic tumor type.29,30,46 Similar prognostication methods should be applied to patients with conjunctival melanoma. Further evaluation of sentinel lymph-node biopsy is also warranted.27,34-38 The search for genetic predictors should continue so that different subgroups of conjunctival melanoma are identified, similar to that seen in uveal melanoma.47 It would be useful to understand why nonbulbar conjunctival melanomas are associated poor rates of survival — that is, whether this is because of genetic differences (possibly related to sunlight exposure) or stromal influences (eg, lymphatic density).

**Systemic Adjuvant Therapy**

In patients known to be at high risk for metastasis, it would be worth undertaking randomized trials of systemic chemotherapy or immunotherapy, similar to those in progress for cutaneous melanoma. Because of the rarity of conjunctival melanoma, it may be possible to enroll patients with conjunctival melanoma in such trials, subsequently performing subgroup analyses.

**Treatment for Metastatic Disease**

Similar to those of systemic adjuvant therapy, clinical trials evaluating treatment for clinical metastases are limited by the rarity of conjunctival melanomas, so investigators should explore the feasibility of enrolling these patients in trials studying cutaneous melanoma.

**Future Directions**

Many patients with conjunctival melanoma experience suboptimal outcomes because of iatrogenic tumor seeding, inadequate local tumor control, and surgical morbidity. The published evidence base is poor, so a need exists for clinical trials and basic science research. Because of the rarity of conjunctival melanoma, multicenter studies are needed. Such collaboration is becoming easier with the development in electronic medical records, automatic extraction of data, and the collaboration of ocular oncology working groups and organizations. Progress should also be encouraged by the formation of patient advocacy groups, which can help raise awareness of the importance of holistic care, emphasizing the need for doctor–patient communication, adequate patient education, informed consent, effective emotional support, and, if necessary, referral to psychology. The greatest improvement in patient care will occur when ocular oncologists are supported by a skilled multidisciplinary team and when biopsy or treatment at nonspecialty centers is no longer considered acceptable.

**References**