



Nina Mikhailenko. *Rainy Day*. Oil on canvas, 16" × 20".

The clinical findings, histopathologic features, differential diagnoses, management, and prognosis of conjunctival melanoma are reviewed.

Malignant Melanoma of the Conjunctiva

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Background: *Conjunctival melanoma is a relatively rare ocular malignancy with substantial associated morbidity and mortality.*

Methods: *More than 100 articles on conjunctival melanoma were reviewed, including most of the relevant recent publications cited in a current MEDLINE search. The author's experience with conjunctival melanomas is also incorporated in this review.*

Results: *Recognition of their precursor lesions at an early stage is important. Staging of the disease by sentinel lymph node biopsy is now advocated in some centers. Surgical excision with adjuvant cryotherapy and alcohol corneal epithelial ectomy is usually effective in eradicating most of these lesions. Extensive cases of flat primary acquired melanosis with atypia may be managed with mitomycin C. Multifocal and advanced melanoma, especially in cases showing intraocular or orbital invasion, may require exenteration and/or radiotherapy to adequately extirpate the neoplasm locally. However, systemic metastases already may have occurred in these patients with advanced disease.*

Conclusions: *Conjunctival melanoma is a condition of concern because of its rarity and lethal potential. Advances in the understanding and management of this neoplasm have markedly reduced the mortality and possibly the morbidity associated with this malignancy.*

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Abbreviations used in this paper: PAM = primary acquired melanosis.

Introduction

Conjunctival melanoma is a relatively rare condition, occurring only 1/40th as often as choroidal melanoma and approximately 500 times less often than cutaneous melanoma. Its incidence is 0.2 to 0.8 per million in white populations.¹⁻⁴ Conjunctival melanoma is a potentially lethal neoplasm, with an average 10-year mortality rate of 30%.¹ It is identified most frequently in the perilimbal interpalpebral bulbar conjunctiva with tumors located in the palpebral or fornical conjunctiva or caruncle, plica semilunaris or eyelid margins having a worse prognosis for survival.^{1,5} Conjunctival melanoma has no sexual predilection, and it is found predominately in middle-aged

and more senior adults; only rare cases have been reported in children.⁶ This condition occurs mainly in the white population, with rare reports in black and other non-white populations. Recent studies have indicated that like cutaneous melanoma, the incidence of conjunctival melanoma is increasing.^{3,4,7}

Similar to cutaneous melanomas, conjunctival melanomas are malignant tumors of proliferating melanocytes that are derived from the neural crest. The conjunctiva is a mucous membrane that covers the anterior half of the pericorneal globe (the bulbar conjunctiva) and lines the posterior surface of the eyelids (the palpebral conjunctiva) forming a fold in the superior and inferior fornices (the forniceal conjunctiva). Since the conjunctival stroma (the substantia propria) contains blood vessels and lymphatics, a malignancy that invades this subepithelial region has the potential for local (“in transit”) and systemic metastases.⁸

The predominant benign conjunctival melanocytic lesions are composed of a variety of nevi and melanoses that also have a predilection for the perilimbal bulbar conjunctiva.^{9,10} Nevi are believed to be congenital lesions that are generally unilateral. They are usually first identified clinically around puberty or early adulthood, with a range from early childhood to the 10th decade of life.^{9,10} They frequently develop cysts and become slightly elevated, and may change in color and size.^{9,10} Dark brown melanotic pigmentation is normally observed in the conjunctiva, a condition referred to as *racial melanosis*, which is especially evident bilaterally from an early age in more heavily pigmented races. This condition is usually in the form of an excess production of melanin or hyperpigmentation by the melanocytes (forming an ephelis) or benign proliferation of melanocytes (forming a benign lentigo).⁹



Fig 1. — Pedunculated black conjunctival mass at superior nasal limbus of right eye of a 76-year-old white woman, who had undergone excision of a smaller pigmented tumor 10 years previously that histopathologically was a malignant melanoma in juxtaposition to a benign-appearing nevus. A similar clinical appearance may occur with a tumor of de novo origin. From Brownstein S, Henry M, Bernardo AI. Malignant melanoma of the conjunctiva after 11 years. *Can J Ophthalmol.* 1979;14:142-146. Reprinted with permission of the *Canadian Journal of Ophthalmology*.

The terminology associated with melanosis is controversial, especially when melanosis is unilateral and acquired, in that this lesion can be a precursor of invasive melanoma. Some authorities have referred to this unilateral acquired pigmentation as *precancerous melanosis*, which in the past has led to inappropriate aggressive therapy — frequently exenteration (surgical excision of the orbital contents, including the eyes and eyelids).¹ As a result, others have referred to these lesions as *benign acquired melanosis*, but this terminology had caused concern that the malignant potential of this condition may be overlooked.^{1,11} Because these lesions may show variable histological findings, the World Health Organization proposed the term *primary acquired melanosis* (PAM) with or without atypia for these lesions (see below).^{1,12,13}

Clinical Findings

Conjunctival melanoma can arise in any region of the conjunctiva but mostly appears in the perilimbal bulbar conjunctiva.¹ It occurs in three clinical settings (in con-

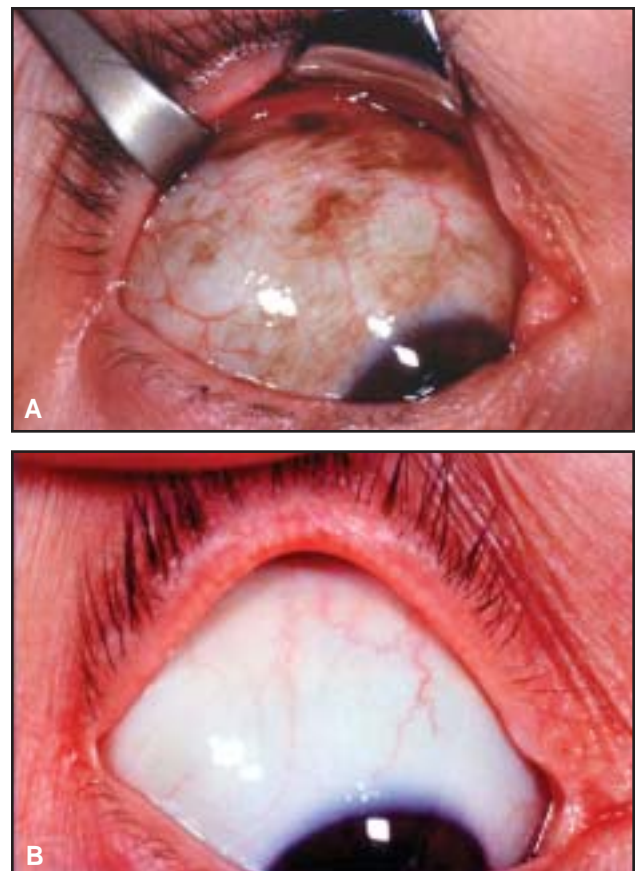


Fig 2. — (A) Extensive PAM of the bulbar, forniceal, and palpebral conjunctiva of the right eye in a 58-year-old white woman. (B) The same patient after 1 year of intermittent topical mitomycin C therapy resulting in the conjunctiva becoming free of melanin pigment and in subsequent map biopsies showing no atypical melanocytes. From Yuen VH, Jordan DR, Brownstein S, et al. Topical mitomycin treatment for primary acquired melanosis of the conjunctiva. *Ophthalmic Plast Reconstr Surg.* 2003;19:149-151. Reprinted with permission.

junction with a nevus, de novo, and PAM with atypia) that are determined in many cases on the basis of histopathologic findings.

In some instances, the tumor occurs in conjunction with a benign-appearing nevus. There may be a history of a preceding, variably pigmented, relatively stationary lesion that subsequently underwent changes in size, shape, and/or color with transformation into a melanoma (Fig 1).^{1,2,14} However, the vast majority of conjunctival nevi, like cutaneous nevi, do not progress to malignant melanoma.

Conjunctival melanoma arises de novo without any preceding lesion in about 12% of patients. Approximately 75% of these neoplasms arise in an area of PAM with atypia that requires histopathologic examination for this diagnosis (Fig 2).^{1,13,15,16} When thickening of the conjunctiva is present in an area of PAM, the development of invasive malignant melanoma is a primary concern (Fig 3), although an inflammatory reaction to the PAM also may produce a similar clinical picture. Furthermore, some of the melanomas associated with PAM also have shown histological evidence of a benign nevus.¹⁶ When PAM occurs as a bilateral condition, it is most often caused by histologically benign racial pigmentation (racial melanosis) that generally occurs in the first decade of life. It is less frequently associated with systemic conditions such as Addison's disease.⁹ Unilateral acquired PAM is more likely due to a proliferation of atypical melanocytes (the histological equivalent of atypical melanocytic hyperplasia, or *melanoma in situ* in dermatopathology) that subsequently can give rise to an invasive malignant melanoma (Fig 3).¹⁵⁻²¹ While PAM without atypia does not progress to a malignant melanoma, almost 50% of cases of PAM with atypia result in an invasive malignant melanoma that may be multifocal within a median of 2.5 years from the time of biopsy for PAM with atypia until progression to melanoma.^{13,15,18} PAM with atypia first presents in the middle-aged and elderly individuals, while pure junctional nevi



Fig 3. — Extensive patches of PAM of the palpebral and bulbar conjunctiva of the left eye with focal pigmented nodules (arrow) in a 28-year-old white woman. From Jakobiec FA, Brownstein S, Wilkinson RD, et al. Combined surgery and cryotherapy for diffuse malignant melanoma of the conjunctiva. *Arch Ophthalmol*. 1980;98:1390-1396. Copyrighted © 1980, American Medical Association. All rights reserved.

occurs almost exclusively in childhood.⁹ PAM without atypia is a frequent clinical finding that is often unilateral. In determining which lesions should be biopsied, clinical judgment based on history, clinical features, and evidence of growth must be used.^{2,22,23} Thirty-six percent of the white population show some degree of PAM that may exhibit slow growth, especially in relation to puberty or pregnancy.²³

Most authorities in ocular oncology advocate that it is safest to biopsy all PAM lesions showing any notable growth.^{22,23}

While many conjunctival melanomas arising de novo or in conjunction with a nevus may show variable or no pigmentation on clinical examination, the majority of the cases of PAM show fairly uniform dark brown pigmentation. However, PAM *sine pigmento* has been named for non-pigmented areas of conjunctiva containing atypical melanocytic cells that may be situated between more heavily pigmented regions or adjacent to an invasive melanoma.^{1,8,24} Also, PAM lesions have been described to “wax and wane” (ie, extend and diminish in size in the horizontal plane).¹²

The corneal epithelium is frequently involved when PAM with atypia is present in the limbal region.^{1,25} Bowman's membrane appears to provide a barrier to invasion beyond the subepithelial region in most cases, but invasive growth into the cornea may occur. Corneal involvement is of importance in designing therapy, particularly with regard to being a risk factor for recurrent disease.

In rare cases, conjunctival melanoma may extend directly into the globe or into the orbit.^{1,14} Clinical metastases usually occur first to the lymph nodes in approximately 45% to 60% of patients with regional metastases.^{26,27} Classically, the medial tumors are believed to spread to the submandibular area and the lateral lesions to the preauricular region (Fig 4).²⁸ More recently, a more complex lymphatic drainage has been described using lymphoscintigraphy in the monkey. Only the medial and central lower eyelid region drained exclusively to the submandibular lymph nodes, while the entire upper eyelid, medial canthus, and lateral lower eyelid drained to the parotid lymph nodes but with the central upper eyelid also draining to the submandibular nodes.²⁸ Eventually, systemic dissemination to many body organs may occur, although this often arises without prior clinical evidence of regional lymph node involvement.^{26,27} Tissues most commonly affected by



Fig 4. — Conjunctival malignant melanoma in a 71-year-old white man with metastases to the preauricular region (P). Courtesy of Dr. J. A. Shields.

metastases include the lung, brain, liver, skin, bone, and the gastrointestinal tract.^{26,27} Lymphatics also have been identified in the human orbit, mainly in the lacrimal gland and dura mater of the optic nerve, but are of questionable importance concerning the intraorbital spread of conjunctiva melanoma.²⁹ In contrast to conjunctival melanoma, the more commonly occurring melanoma of the uveal tract metastasizes almost exclusively hematogenously, especially to the liver.¹

Histopathology

The handling of the specimen obtained by wide surgical resection with a “no touch” minimal tumor manipulation technique has been described in detail.^{30,31} The histogenesis of conjunctival melanoma is often determined histopathologically and includes nevi (which also may be associated with PAM with atypia), de novo, and mostly PAM with atypia.^{1,2,16} The histopathologic diagnosis of malignant melanoma of the conjunctiva requires recogni-

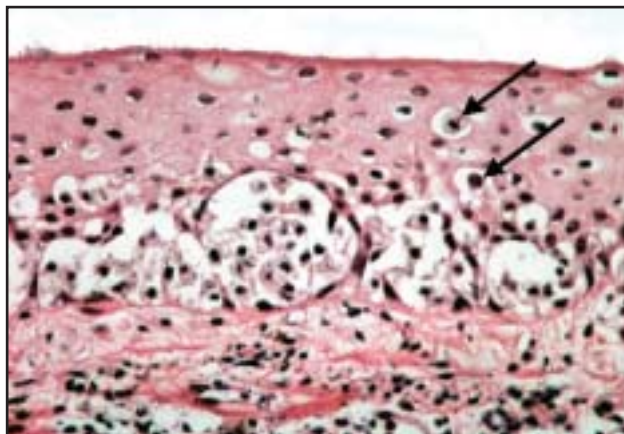


Fig 5. — Histopathologic section from a patient with PAM with atypia of the conjunctiva (same patient as in Fig 3) shows prominent nests of atypical melanocytes in the junctional region with pagetoid invasion (arrows) of the overlying epithelium (hematoxylin and eosin, $\times 250$).

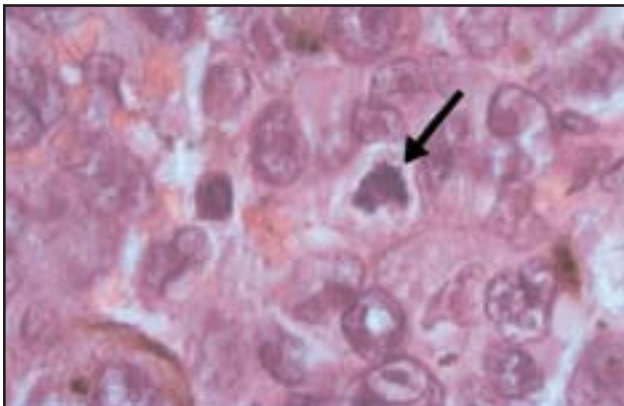


Fig 7. — Histopathologic section of a recurrent malignant melanoma of the superior forniceal conjunctiva shows a large cluster of epithelioid cells with an atypical mitosis (arrow) in the substantia propria (hematoxylin and eosin, $\times 1000$).

tion of atypical melanocytes that may vary from obvious to extremely subtle. In cases in which no consensus diagnosis can be reached, an “indeterminate” or borderline diagnosis may be required.^{32,33}

The atypical melanocytes of both PAM with atypia and invasive malignant melanoma of the conjunctiva may show prominent nesting in the junctional region with pagetoid extension of individual or groups of tumor cells into the overlying epithelium (Figs 5 and 6).¹² When epithelioid cells showing pleomorphic nuclei, prominent nucleoli, atypical mitoses, and abundant cytoplasm are evident, the diagnosis is more obvious (Figs 6 and 7).¹²

The diagnosis of invasive malignant melanoma is established with invasion of the underlying substantia propria of the conjunctiva by atypical tumor cells, especially when there is loss of the maturation that is found in most nevi of superficial plump cells to more deeply situated spindle cells (Figs 7 and 8).⁹ The thickness of the tumor, which is determined by measuring from the epithelial surface to the deepest extent of the neoplasm in the substantia propria, is of prime prognostic importance.^{1,2}

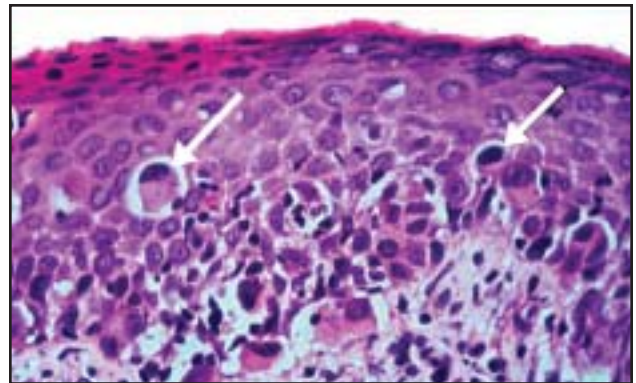


Fig 6. — Histopathologic section shows epithelioid melanoma cells in the junctional region of the conjunctiva with pagetoid invasion (arrows) of the overlying epithelium (hematoxylin and eosin, $\times 400$). From Jakobiec FA, Brownstein S, Wilkinson RD, et al. Adjuvant cryotherapy for focal nodular melanoma of the conjunctiva. *Arch Ophthalmol.* 1982;100:115-118. Copyrighted © 1982, American Medical Association. All rights reserved.

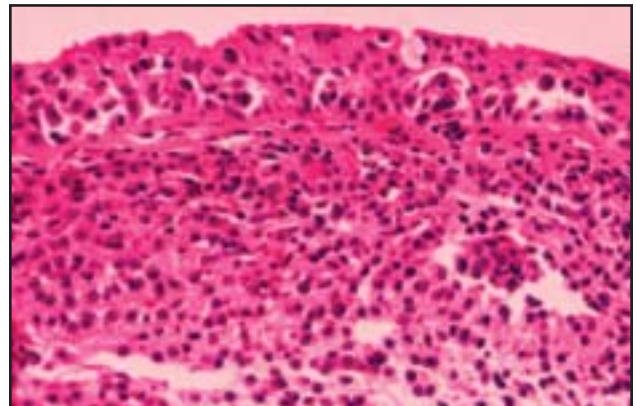


Fig 8. — Histopathologic section of superior palpebral conjunctiva (taken from a dark brown nodule depicted by the arrow in Fig 3) shows PAM with atypia and invasive malignant melanoma of the adjacent substantia propria (hematoxylin and eosin, $\times 250$).

In cases where a diagnosis based on the histopathologic findings is uncertain, including after prolonged bleaching of the sections to examine nuclear details, immunohistochemical staining may be helpful. Our laboratory has demonstrated that HMB-45 immunoreactivity is the most specific of the multiple antibodies currently available for the demonstration of the atypical melanocytes in PAM with atypia.³⁴ This is especially helpful when the vector red substrate method is utilized in contrast to the more popular brown staining by the diaminobenzidine substrate. The latter immunostain may appear similar to melanin pigment in the examined melanocytic cells.

Differential Diagnosis

A number of clinical entities are considered in the differential diagnosis of conjunctival melanoma. The most common are conjunctival nevi, particularly those that show growth and have atypical features. Since in rare cases a conjunctival nevus is a precursor lesion for a malignant melanoma, any pigmented lesion of the conjunctiva showing growth and/or atypical features should be considered for excisional biopsy. Approximately 8% of conjunctival nevi have been found to grow.¹⁰ The presence of intralesional cysts is an important differentiation finding as these cysts are present mainly in conjunctival nevi and only rarely within a malignant melanoma, usually in association with a conjunctival nevus.¹⁰

Other lesions that may simulate conjunctival melanoma include extraocular extension of a uveal malignant melanoma, metastatic malignant melanoma to the conjunctiva (usually from a cutaneous origin), melanosis oculi and oculodermal melanocytosis (nevus of Ota), scleral-uveal staphyloma, foreign body, polymerized epinephrine, nerve loop of Axenfeld, amyloidosis, ochronosis, pigmented epithelial tumors including papilloma and squamous cell carcinoma, and pigmented pinguecula including in Gaucher's disease.^{1,9,13} Melanosis oculi and oculodermal melanocytosis should be readily differentiated clinically from PAM by the presence from birth of usually unilateral, subconjunctival/episcleral slate-gray or blue areas (Tyndall effect) instead of a brown-black lesion that characterizes PAM.^{9,20} Furthermore, the former lesions do not move with the overlying conjunctiva and are associated with a more heavily pigmented uveal tract. There is a higher incidence of melanoma, particularly of the uvea, in white patients with melanosis oculi and oculodermal melanocytosis.³⁵ Glaucoma has been reported to occur more frequently in oculodermal melanocytosis.³⁶

Management

The preferred management of conjunctival melanoma, as with most malignant tumors, is total surgical excision.^{30,31}

Unfortunately, the extensive horizontal and even vertical growth of this neoplasm does not always lend itself to simple excision — short of an orbital exenteration, which was often the recommended treatment until the 1980s. Many patients and surgeons preferred to avoid orbital exenteration because of the patient's loss of visual function and poor cosmetic appearance. In advanced cases (eg, deeply invasive and multifocal tumors), exenteration of the orbital contents may be the only option, although by this stage systemic spread of the tumor has frequently occurred, resulting in no effect on the prognosis for survival.³⁷ Others have advocated irradiation therapy as an alternative to exenteration for excellent local control and cosmesis.³⁸

In patients with extensive and multifocal neoplasia, cryotherapy has decreased the risk of local recurrence after surgical excision of nodular tumors. Cryotherapy is applied to the margins and at times to the base of the excised regions.^{1,2,8,17,18,39,40} Because a frequent cause of recurrent tumor at the limbus is corneal PAM with atypia, the affected cornea is treated with chemical applications of absolute alcohol to the denuded Bowman's layer in order to devitalize any residual atypical melanocytes.⁴⁰ When deeper involvement of the cornea is clinically apparent, en bloc lamellar keratectomy with excision of the adjacent limbal and conjunctival neoplasm has been advocated.^{30,31} Furthermore, it has been suggested that after recurrent disease, patients with this relatively rare tumor should be managed in specialized ocular oncologic centers to minimize the incidence of further recurrences, which have been as high as 62%.^{1,2}

Others have advocated treatment with the CO₂ laser instead of or in addition to cryotherapy.⁴¹ Some centers have successfully utilized radiation therapy in the form of brachytherapy with iodine, strontium, or ruthenium plaques, or with external beam or proton beam irradiation.^{37,42,43} More recently, topical chemotherapy with mitomycin C has been used to eradicate the atypical melanocytes in cases with extensive PAM with atypia (Fig 2).^{44,46} A combination of surgical excision of nodular tumors with cryotherapy to the underside of the adjacent conjunctival margins, localized alcohol corneal epitheliectomy in the areas of corneal pigmentation, and postoperative topical mitomycin C have been recommended for the management of extensive cases with invasive disease.^{30,31,47}

It has been proposed that excision of the sentinel lymph nodes allows for better staging and possibly early detection of micrometastases to the regional lymph nodes, as has been demonstrated in patients with cutaneous melanoma.⁴⁸⁻⁵⁰ With documented neoplastic spread to the regional lymph nodes, resection of all of the lymph nodes in the ipsilateral head and neck is indicated.^{2,8} Patients with initial lymph node metastases have a better prognosis than those presenting initially with systemic metastases.²⁶ Once systemic disseminated metastases have been identified, the management is under the auspices of oncologists, who may offer chemotherapy

and/or biochemotherapy, usually with a poor prognosis for survival of the patient.^{1,26} Recommended biannual assessments include a complete clinical examination, magnetic resonance imaging and/or computed tomography examinations of the brain, chest, abdomen, and pelvis, and laboratory tests, especially concerning hepatic function.²⁶ The TNM (tumor, lymph node, metastasis) staging classification has been modified from the International Union Against Cancer.¹ Furthermore, patients with ocular melanoma, including conjunctival melanoma, have an increased risk to develop cutaneous melanoma and dysplastic nevi; thus it is recommended that they have regular dermatological examinations.^{51,52}

Prognostic Features

The mortality rate of conjunctival malignant melanoma is approximately 30% (ranging from 9% to 61% in the reviewed literature) on a long-term follow-up.^{1,5,16,53-57} Prognostic factors include clinical features, with tumor location and extent being of major importance. Patients with multifocal tumors, orbital invasion, recurrent disease, and involvement of the caruncle, plica semilunaris, eyelid margins, and the palpebral and forniceal conjunctiva have a worse prognosis for survival.^{1,5,16,53-57} The mortality rate has been shown to be approximately equal in patients



Fig 9. — A 69-year-old white man who 2 years earlier underwent excision and cryotherapy of a bulbar conjunctival malignant melanoma located inferonasally on the right eye with the subsequent development of an epibulbar recurrence and a pigmented eyelid margin nodule. The latter was found to be an in-transit intralymphatic metastasis from the epibulbar tumor, as histopathologic examination of a full thickness eyelid excision showed no intraepithelial melanocytic involvement overlying the nodule of tumor, which was present in the dermis and orbicularis muscle. Regional metastases to the preauricular and cervical lymph nodes subsequently occurred and was managed with radical neck dissection and parotidectomy. From Jakobiec FA, Rini FJ, Fraunfelder FT, et al. Cryotherapy for conjunctival primary acquired melanosis and malignant melanoma: experience with 62 cases. *Ophthalmology*. 1988;95:1058-1070. Reprinted with permission from the American Academy of Ophthalmology.

with conjunctival melanoma in association with and without PAM with atypia.^{13,16}

Histopathologic findings associated with a poor prognosis include a tumor thickness of greater than 0.8 mm (in contrast to 1.5 mm or 2 mm in different studies) and involvement of the surgical margin.^{1,5,12,16,53-57} Findings indicating poor prognosis include presence of a dominant pagetoid or melanoma in situ growth pattern, PAM sine pigmento, lymphatic or vascular invasion, presence of epithelioid cells, and 5 or more mitoses per 10 high-power fields.^{5,8,16} Patients with in-transit metastases (regional periocular metastases), which may be identified clinically (Fig 9) and confirmed histologically, also have a poor prognosis, with the subsequent development of systemic metastases in most of these cases.^{1,8}

Conclusions

Conjunctival malignant melanomas are relatively rare tumors, but they are important because of their potential to cause death. It is essential to recognize their precursor lesions, including PAM with atypia and an enlarging or atypical nevus, at an early stage. Staging of the disease by sentinel lymph node biopsy is now advocated in some centers. Surgical excision with adjuvant cryotherapy and alcohol corneal epitheliaectomy is usually effective in eradicating most of these lesions. Extensive cases of flat PAM with atypia may be managed with mitomycin C. Multifocal and advanced melanoma, especially in cases showing intraocular or orbital invasion, may require exenteration and/or radiotherapy to adequately extirpate the neoplasm locally. However, systemic metastases already may have occurred in these patients with advanced disease.

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