NEOPLASTIC DISORDERS OF VISUAL APPARATUS IN CLINICAL OPTOMETRY: ADVANCES AND MANAGEMENT

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ABSTRACT

Ocular neoplasms, both primary and metastatic, may present with visual disturbance or vision loss and often are asymptomatic. Clinical examination may demonstrate leukocoria, abnormal pupillary light reflex, or a mass lesion with or without retinal detachment or hemorrhage. Retinoblastoma in children and uveal melanoma and ocular metastases in adults are the most important ocular malignant neoplasms referred for imaging to aid with diagnosis and staging. Familiarity with their common imaging appearances, the common patterns of spread, and the diagnostic findings of greatest concern to the optometrist or ocular oncologist will enhance accuracy of imaging interpretation. Clinical examination and imaging using B-scan ultrasound, A-scan ultrasound, fluorescein angiography, computed tomography and magnetic resonance imaging have complementary roles in ocular tumor staging and treatment assessment. Ocular neoplasm tumors are relatively rare but require unique diagnostic and treatment considerations given the functional importance of the eye and periocular structures and their unique metastatic behavior. In the following paper, a major malignant tumor of the ocular adnexa including the eyelid, conjunctiva and orbit will be reviewed. Frozen section control of the margins and, in selected cases, Mohs microsurgery have decreased the recurrence rate in malignant eyelid tumors. Intraoperative cryotherapy and postoperative topical mitomycin C have similarly contributed to better surgical outcomes in conjunctival malignant tumors including squamous cell carcinoma and malignant melanoma. Immunotherapy with CD20 antibodies is a developing treatment in Ocular neoplasm lymphomas. Optometrists by the new advances in clinical optometry research, and specialists in occuloplasty / ocularistry form part of the team for a multidisciplinary approach in the clinical management of neoplastic disorders of visual apparatus.

INTRODUCTION

Malignant Ocular neoplasm tumors comprise a diverse group of disorders. Ocular neoplasms, both primary and metastatic, may present with visual disturbance or vision loss and often are asymptomatic. Clinical optometric examination may demonstrate leukocoria, abnormal pupillary light reflex, or a mass lesion with or without retinal detachment or hemorrhage. Retinoblastoma in children and uveal melanoma and ocular metastases in adults are the most important ocular malignant neoplasms referred for imaging to aid with diagnosis and staging. Familiarity with their common imaging appearances, the common patterns of spread, and the diagnostic findings of greatest concern to the ocular oncologist will enhance accuracy of imaging interpretation. Clinical examination and imaging using B-scan ultrasound, A-scan ultrasound, fluorescein angiography, computed tomography and magnetic resonance imaging have complementary roles in ocular tumor staging and treatment assessment.

Malignant Eyelid Tumors and Predisposing Lesions: Basal Cell Carcinoma

Clinical Features. Basal cell carcinoma (BCC) is the most common malignant eyelid tumor, accounting for 85% of all such tumors (Alizadeh *et al.*, 1994). The tumor usually affects adults but may also occur in younger patients. Basal cell carcinoma arises in sun-exposed skin, implying that actinic damage is important in the pathogenesis. Basal cell carcinoma involves the lower eyelid in 55% of patients, the medial canthus in 30%, the upper eyelid in 10% and the lateral canthus in 5% (Lai *et al*., 2017). When BCC involves the eyelid margin, there is loss of lashes.

Clinically, there are two distinct types of BCC, nodular and morphea. The nodular type usually presents as an elevated mass with fairly well-defined margins (Figure 1). Ulceration may develop. The morphea form type, by contrast, has poorly defined borders and usually lacks ulceration. It is difficult to judge clinically where the margins of a morphea form BCC are located.

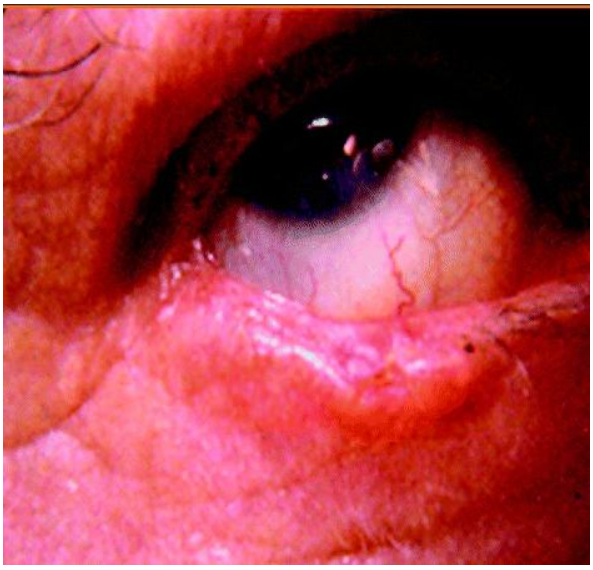

Figure 1: Nodular basal cell carcinoma of the lower eyelid.

Overall, 0.7% of basal cell tumors are a result of nevoid BCC syndrome (Gorlin-Goltz syndrome), an autosomal dominant disease (Wang, *et al*., 2008).

Patients with this syndrome have multiple basal cell tumors, odontogenic keratocytes, bifid ribs, and palmar and plantar pits.

Histologic Features: Basal cell carcinoma is composed of cords of tumor cells with closely packed nuclei embedded in a dense fibrous tissue stroma. Deeper invasion into dermis may be seen with the morphea form type. There are several histopathologic variants of BCC, including the pigmented type, which contains melanin and thus can be confused with nevus or malignant melanoma. For treatment and prognosis, the best treatment option for BCC is complete surgical excision of the tumor with frozen section control of the surgical margins (Scott *et al.*, 2003). Mohs micrographic surgery can also be used for control of tumor margins.

The eyelid defect created by tumor excision can be repaired. Modern oculoplastic surgical techniques can be used to repair a total full-thickness defect of the lower eyelid successfully (Boukes, and De Vries-Knoppert, (1985). Repair of upper eyelid defects may be more challenging but can usually be accomplished using two-stage eyelid-sharing procedures. In cases of locally advanced BCC with post septal orbital invasion, orbital exenteration may be necessary(Shinomiya *et al*., 2013). External-beam radiation therapy may be appropriate for recurrent or extensive BCC that may not be amenable to complete surgical excision, or in patients who are poor candidates for surgery. Regional lymph node involvement or systemic metastasis secondary to BCC is extremely rare. However, local recurrence may occur and is more frequent in incomplete excisions, in the setting of inner canthus and morphea form-type tumors.

Preliminary studies using retinoids (etretinate and isotretinoin) in the management of BCC have yielded variable results (Thomas and Kaliamurthy, 2013). A new class of immune-response modifier, represented by topical imiquimod cream was demonstrated to have some potential effect in the topical treatment of BCC, either alone or in combination with retinoids (Ebrahimiadib *et al*., 2016). Photodynamic therapy (PDT) is a new non-invasive procedure that produces tumor destruction. However, although PDT with α-amino levulinic acid is a promising approach into therapy of dermal lesions, it is not yet an acceptable alternative in the treatment of BCC of the eyelids (Csepregi *et al*., 2018).

Keratoacanthoma

Clinical Features: Keratoacanthoma usually presents as a rapidly growing solitary nodule (Siagris *et al.*, 2012). There is a distinctive central crater containing keratin debris. Keratoacanthoma usually occurs in immunocompromised patients and is possibly of viral origin. Regarding its pathology, Keratoacanthoma resembles low-grade squamous cell carcinoma (SCC), except for the presence of a central keratin-filled crater (Hardy *et al.*, 2017). It shows acanthotic and dyskeratotic epithelium resembling SCC and is usually associated with an inflammatory cell response. For treatment, Keratoacanthoma is believed to represent a variant of SCC. Excisional biopsy is usually recommended. If there is uncertainty about the diagnosis, stationary lesions can be carefully observed (Jain *et al*., 2004). Keratoacanthoma may regress spontaneously over a period of 3 to 6 months.

Squamous Intraepithelial Neoplasia

Clinical Features: Squamous intraepithelial neoplasia (Bowen's disease) is considered to be squamous carcinoma in situ. It occurs most commonly in fair-skinned elderly individuals who have a history of chronic sun exposure. The majority of the patients are 60 years or older. Periocular squamous intraepithelial neoplasia occurs most frequently in the lower eyelid. It most often appears as a painless, elevated nodular or plaque-like lesion with chronic scaling and fissuring of the skin. Additional presenting features include a papillomatous lesion, a cutaneous horn and a large ulcerated lesion (Shields *et al.*, 2004).

Pathology

There is marked squamous dysplasia without invasion beyond the basement membrane. Lipid or immune histo-chemical stains may be necessary to differentiate between squamous intraepithelial neoplasia and intraepithelial spread of sebaceous gland carcinoma. The treatment strategy for squamous intraepithelial neoplasia consists of wide excision with clear margins, similar to that for SCC (Lowe *et al*., 2012).

Actinic Keratosis

Clinical Features: Actinic keratosis is a premalignant cutaneous lesion that predisposes to the development of SCC (Smoker *et al.*, 2008). Actinic keratosis generally occurs in older fair-skinned individuals with a history of chronic sun exposure and usually presents as multiple slightly elevated erythematous lesions with patchy areas of ulceration. Histologic Features, Actinic keratosis is characterized by elastotic degeneration of the dermis, hyperkeratosis and elongation of the rete pegs of the skin. For Treatment and Prognosis, surgical resection of actinic keratosis may be the treatment of choice before transformation into SCC (Lowe *et al*., 2012). Topical chemotherapy with 5-fluorouracil (Effudex) may be appropriate in some clinical situations.

Squamous Cell Carcinoma

Clinical Features: Squamous cell carcinoma accounts for less than 5% of all malignant eyelid tumors (Sepahdari *et al*., 2010). In some series, SCC is the second most common malignant eyelid tumor after BCC; in other series, SCC is third most common, after sebaceous cell carcinoma (Ansari & Mafee, 2005). SCC can arise from a pre-existing actinic keratosis, Bowen's disease, keratoacanthoma, radiation dermatitis or de novo (Zhang *et al*., 2015). SCC may present as an elevated keratinized mass similar in appearance to BCC (Figure 2).

Histologic Features: Squamous cell carcinoma is comprised of proliferating malignant squamous cells with increased mitotic activity. In invasive SCC, tumor cells are seen below the epidermis. More differentiated tumors may produce keratin.

Treatment and Prognosis

The surgical principles as outlined for BCC also apply to SCC. Determination of tumor margins during surgical excision may be more difficult with SCC than with BCC, as

SCC tends to have more ill-defined margins. SCC is associated with a risk of regional lymph node metastasis. For periocular SCC, the risk of regional lymph node metastasis may be as high as 20-30%, (Ioannidis *et al.*, 2018). Sentinel lymph node biopsy may be considered in high-risk patients, such as recurrent lesions or those with SCC greater than 2cm in diameter or perineural invasion (Bacman *et al.*, 2018). SCC is also associated with a risk of metastasis to distant organs, which increases with these high-risk features. Photodynamic therapy is emerging as a promising treatment for patients with multiple or large SCC in whom surgery is not appropriate. In such cases, PDT is associated with reasonable efficacy, good cosmesis and limited morbidity (Vemuganti *et al.*, 2012). However, the precise role of PDT remains uncertain at this time.

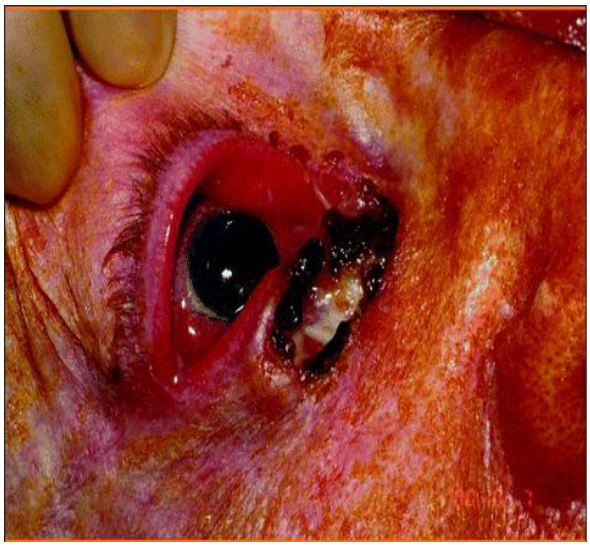

Figure 2: Squamous cell carcinoma of the lower eyelid margin.

Sebaceous Gland Carcinoma

Clinical Features: Sebaceous gland carcinoma (SGC) accounts for approximately 5% of all malignant eyelid tumors. SGC can originate from Meibomian, Zeis or the sebaceous glands of the caruncle. It may be multicentric in origin (Shields *et al.*, 2004). Sebaceous gland carcinoma is more common in the upper eyelid but can also occur in the lower eyelid. It usually presents as a solitary yellow nodule resembling a chalazion. The pagetoid variety of SGC may resemble blepharon conjunctivitis in its clinical presentation. Like other malignant eyelid tumors, SGC may be associated with loss of lashes. SGC can invade and replace eyelid skin and conjunctival epithelium in a pagetoid fashion. The infiltrated epithelium is thickened and sometimes totally replaced by the tumor cells. Delayed or mistaken diagnosis is very common and thus locally advanced cases are not uncommon (Bouhout *et al.*, 2017). If left untreated, the tumor has the ability to infiltrate post septal orbital structures, including the lacrimal gland.

Patients with SGC should be screened for Muir-Torre syndrome, a rare autosomal dominant syndrome consisting of sebaceous gland tumors (hyperplasia, adenoma or carcinoma) and internal malignancies (colon cancer and other malignancies) (Croxatto and Font, 2018). A baseline colonoscopy, a gynecologic examination in women and other baseline imaging studies, to rule out other associated malignancies, are indicated at the time of initial diagnosis of SGC.

Histologic Features

Sebaceous gland carcinoma is composed of lobules or sheets of large, pleomorphic tumor cells with a foamy cytoplasm due to lipid vacuoles. The lipid can be demonstrated using special lipid stains such as Oil-red-O on fresh tissue that has not been formalin fixed. The central cells of SGC express human milk fat globulin (HMFG)-1 and epithelial membrane antigen (EMA), whereas the small peripheral basal and duct cells generally express cytokeratin. SGC also expresses Cam 5.2 and anti-BCA-255 (BRST-1), whereas BCC expresses neither EMA nor BRST-1 and SCC expresses EMA but not Cam 5.2 (Croxatto and Font, 2018). Therefore, a tumor that stains with EMA and Cam 5.2 is most likely to be SGC.

Treatment and Prognosis: The management of SGC consists of complete surgical excision with control of margins (Gengler and Guillou, 2006). There is controversy as to whether frozen sections, or Mohs surgery is preferable or if it is better to wait for permanent sections as it is difficult to diagnose SGC in frozen sections. Map biopsies of the eyelids and conjunctiva are obtained to rule out pagetoid involvement (Park and Araujo, 2009).

In the case of diffuse pagetoid intraepithelial neoplasia of the conjunctiva or eyelids and in the case of post-septal orbital invasion, orbital exenteration may be indicated as the best way to achieve local control. External-beam radiation therapy should be reserved for cases of recurrent or locally advanced disease, in which complete surgical excision cannot be accomplished and for patients who are poor candidates for extensive surgery. Topical chemotherapy with mitomycin C (MMC) has also been used successfully for the treatment of intraepithelial neoplasia (Raskin *et al.*, 2015). Close follow-up is necessary because SGC is associated with a high risk of local recurrence, particularly if inadequately treated, and a risk of regional lymph node metastasis of approximately 10% according to most series. SGC can metastasize to distant organs such as the lung, liver, brain and skull. According to the Armed Forces Institute of Pathology (AFIP), the tumor-related mortality rate in patients with SGC is 15% (Politi *et al.*, 2010). A more recent series by Shields and colleagues suggests a lower mortality rate, of less than 10%.(Lloyd, 2001) Patients with the pagetoid variety have a worse prognosis.

Cutaneous Melanoma of the Eyelid and Periocular Region

Clinical Features: Cutaneous melanoma of the eyelid is relatively rare, accounting for fewer than 1% of all eyelid malignancies (Boukes and De Vries-Knoppert, 1985). Clinically, melanoma of the eyelid presents as a variably pigmented eyelid nodule and may demonstrate progressive growth. Periocular melanoma usually occurs in the malar region over an area of lentigo melanoma.

Histologic Features: Cutaneous melanoma is composed of neoplastic melanocytes (Rasmussen *et al.*, 2011). All three histologic subtypes of melanoma (nodular, superficial spreading and lentigo maligna) can occur in the periocular region. Several studies have demonstrated that as with cutaneous melanomas in other locations, tumor thickness is an important predictor of regional lymph node metastasis and survival in patients with eyelid melanoma (Avery *et al*., 2011).Clark's micro staging does not apply to eyelid skin because the dermis is not stratified in papillary and reticular zones in this location, and there is no subcutaneous fat in the eyelid. The major prognostic parameter is the depth of invasion as measured from the top of the granular layer of the epidermis to the point of deepest invasion into the dermis.

Treatment and Prognosis: Management of eyelid and periocular melanoma is similar to management of other cutaneous melanomas. Wide surgical excision is the treatment of choice for local control. Control of surgical margins should be done but there is controversy about which technique is better. Frozen sections are controversial because they can induce some difficulties in the diagnosis. Mohs surgery (via serial mapped excision) may also be useful. In the head and neck in general, and in the periocular region in particular, the WHO recommendation of at least 1 cm margins for melanomas less than or equal to 1 mm is not always possible if the goal is preservation of the globe and its function (Boukes and De Vries-Knoppert, 1985). Most surgeons aim for a 4-5 mm tumor-free margin on permanent formalin-fixed sections (Kornreich *et al*., 2001).

A patient with a newly diagnosed eyelid melanoma should undergo ultrasonography of the regional lymph nodes to rule out clinically positive lymph nodes. The role of sentinel lymph node biopsy for more accurate staging of the regional lymph nodes has evolved in the last decade (Ansari and Mafee, 2005). Eyelid melanomas are associated with a risk of distant organ metastasis, which can occur years after the initial diagnosis; thus, careful, long-term follow-up is prudent.

Merkel Cell Carcinoma

Clinical Features: Merkel cell carcinoma is a malignant tumor that arises from Merkel cells (mechanoreceptors for touch). The tumor generally occurs in older patients. Clinically, Merkel cell carcinoma usually presents as a reddish-blue lesion(Newman *et al.*, 2011). It usually occurs in the upper eyelid but can also occur in the lower eyelid or in the periocular skin. The tumor has a tendency to metastasize to the regional lymph nodes in about 30-50% of the cases.

Treatment and Prognosis: Wide surgical excision followed by external-beam radiation therapy to the primary site is probably the best treatment although there is not enough information to assume that one particular approach is better than the other (Valvassori *et al.*, 2019). Owing to the relatively high risk of regional lymph node metastasis (30-50%), consideration should be given to treatment of the regional lymph nodes (Avery *et al*., 2011). In selected cases, adjuvant chemotherapy may be recommended even in the absence of clinical evidence of metastasis at the time of initial diagnosis (Ahmed *et al*., 2008).

Metastatic Eyelid Tumors

Clinical Features: Metastatic eyelid tumors can originate from a variety of primary cancers including breast, lung and kidney, or from cutaneous melanoma (Gengler and Guillou, 2006). The eyelid mass may be the first sign of malignancy but is more commonly a new focus of metastasis in a patient with poorly controlled cancer at another site. Metastatic eyelid tumors are characterized by a growing eyelid nodule that may be mistaken for an inflammatory lesion.

Treatment and Prognosis: An incisional/excisional biopsy to establish the tumor diagnosis and to remove the lesion for palliative purposes may be appropriate (Ebrahimiadib *et al*., 2016). In patients who are poor candidates for surgery, external beam radiation therapy in addition to chemotherapy may also be used as a palliative measure.

Malignant Conjunctival Tumors and Predisposing Lesions:

Ocular Surface Squamous Neoplasia

Ocular surface squamous neoplasia (OSSN) is currently the preferred term for premalignant and malignant epithelial lesions of the cornea and conjunctiva.

Clinical Features: Ocular surface squamous neoplasia has been associated with UV exposure, smoking, human papillomavirus types 16 and 18 and immunodeficiency, including immunodeficiency resulting from HIV infection (Tzioufas and Voulgarelis, 2007). A history of actinic skin lesions, such as solar keratosis and SCC is also strongly associated with the development of OSSN. OSSN usually presents as a fleshy limbal mass in the interpalpebral fissure (Figure 3). Rarely, the lesion involves the fornices. Clinically, the lesion may demonstrate leukoplakia (hyperkeratosis) on the surface and may appear papillomatous. The tumor can have prominent feeder vessels.

Figure 3: Conjunctival squamous cell carcinoma of the paralimbal region.

Histologic Features: Ocular surface squamous neoplasia consist of neoplastic cells arising in the conjunctival epithelium. Conjunctival intraepithelial neoplasia consists of partial displacement of epithelium by neoplastic cells. Invasive OSSN breaches the basement membrane and invades the conjunctival stroma. Specific variants of OSSN include mucoepidermoid carcinoma and spindle cell carcinoma, which are more invasive than other variants of OSSN (Parment, 1997).

Treatment and Prognosis: The treatment of OSSN varies with the size and location of the tumor, but the primary modality is complete surgical excision with cryotherapy applied to the excision margins (Shields and Shields, 1993). In cases with widespread involvement of the conjunctival surface, it may be difficult to excise the tumor in one piece. Complete excision of the tumor may require a lamellar sclero-conjunctivectomy or a lamellar keratectomy at the limbus. After removal of the tumor, double freeze-thaw cryotherapy is applied to the conjunctival margins, and the conjunctiva is closed using absorbable sutures.

Topical chemotherapy with MMC (0.02-0.04%) or 5-fluorouracil (1%) can be used as postsurgical adjuvant therapy or to eradicate conjunctival intraepithelial neoplasia (Tzioufas and Voulgarelis, 2007). Some investigators employed interferon-α 2b via intralesional injection or via drops with complete resolution of the OSSN (Onyemocho *et al*., 2013). Irradiation in the form of episcleral plaque brachytherapy or proton-beam therapy has also been used in cases of recurrent or extensive disease (Korsten *et al*., 2017). Ocular surface squamous neoplasia rarely invades the globe or orbit. In such cases, enucleation or orbital exenteration may become necessary to fully eradicate the tumor. The risk of regional lymph node metastasis associated with OSSN is estimated to be less than 10%. Distant metastasis is rare. Owing to the high-risk of recurrence after treatment, long-term follow-up is necessary.

Conjunctival Primary Acquired Melanosis and Melanoma

Clinical Features: Primary acquired melanosis (PAM) presents as flat, diffuse or patchy areas of hyperpigmentation in the conjunctiva that moves over the sclera. In contrast to the conjunctival nevus, the lesion has no cysts in clinical examination. PAM can demonstrate a 'waxing and waning phenomenon' whereby the pigmentation in the lesion seems to vary over time. PAM can also be partially or totally amelanotic (sine pigmento). This may create difficulty in determining the clinical margins of the lesion.

Histo-pathologically, PAM is divided into two major groups: PAM without atypia and with atypia. PAM with atypia is characterized by the presence of atypical melanocytes that have different sizes and shapes. Primary acquired melanosis of the conjunctiva has an average risk of 30% of evolution into a conjunctival melanoma. In PAM with atypia the risk is higher, at 45% (Raskin *et al.*, 2015). In contrast to the much quoted AFIP series, recent data suggest that evolution of PAM into conjunctival melanoma is significantly lower at 8% at 5 years (Newman *et al.*, 2011).

Conjunctival melanoma can originate from a pre-existing nevus, from PAM or de novo (Kornreich *et al*., 2001). The factors predisposing to the development of conjunctival melanoma are not known. Primary acquired melanosis with atypia is associated with a higher risk of malignant transformation into a conjunctival melanoma than are conjunctival nevi. Clinically, conjunctival melanoma presents as a variably pigmented mass (Figure 4). Some tumors are amelanotic. Recurrent melanomas in particular have a tendency to be amelanotic and may present as a subconjunctival amelanotic mass in the eyelid. Conjunctival melanomas can be associated with prominent feeder vessels involving the corneal limbus, palpebral or forniceal conjunctiva. In locally advanced cases, conjunctival melanoma can invade the globe and the orbit.

Figure 4: Conjunctival melanoma involving the bulbar conjunctiva and the corneal limbus.

Histologic Features: Histo pathologically, PAM presents flat, brown intraepithelial lesions. It has been shown that with immunostaining for Ki-67 and proliferating cell nuclear antigen, PAM with atypia had significantly higher

proliferation activity than PAM without atypia (Taneja *et al*., 2013). Furthermore, there is a higher expression of human melanoma black (HMB)-45 in PAM with atypia compared with PAM without atypia and conjunctival nevi (Vemuganti *et al*., 2012).

Conjunctival melanoma is composed of malignant melanocytes with a spindle or epithelioid appearance. Tumor thickness is of great importance in predicting the risk of metastasis and survival and for selecting patients who may be candidates for sentinel lymph node biopsy.

Treatment and Prognosis: With PAM, there are certain features that necessitate treatment. Corneal involvement, palpebral involvement, more than 2 clock hours of involvement and elevation of the lesion are some of the features that necessitate treatment (Levitt *et al*., 2015). Treatment usually involves superficial alcohol keratectomy, excision of the highly suspicious nodule, quadrantic map biopsies and cryotherapy from underside of the conjunctiva. Topical chemotherapy using MMC 0.04% can be used as primary or supplemental treatment for extensive PAM (Bolaños-Jiménez *et al*., 2015).

Treatment of conjunctival melanoma consists of complete surgical excision with cryotherapy applied to the excision margins (Croxatto and Font, 2018). Alcohol epitheliectomy and partial lamellar keratectomy may be necessary for lesions near the limbus involving the cornea. Adjuvant radiation therapy can be considered, depending on the location and extent of the tumor and may be delivered in the form of strontium applicators, radioactive plaques, or proton-beam radiation therapy (Gengler and Guillou, 2006). Some investigators advocate treating primary acquired melanosis with topical chemotherapy as long as the invasive component is removed surgically. Topical MMC 0.04% chemotherapy may also be used for postsurgical treatment of invasive tumors after complete surgical resection, although which end points to use to measure efficacy in this setting are difficult to determine (Goldsmith *et al*., 2001). Owing to the high recurrence rate after treatment, extended follow-up is necessary.

Orbital exenteration may become necessary in patients who experience multiple local recurrences or with diffuse involvement of the conjunctiva and eyelid, or in patients not willing to come in for the necessary frequent follow-up visits. Orbital exenteration does not improve survival and is therefore performed only to achieve local control (Demirci *et al.*, 2008).

Conjunctival melanoma spreads to regional lymph nodes in 15-30% of patients (Levitt *et al.*, 2015), therefore, sentinel lymph node biopsy at the time of primary resection of the conjunctival melanoma may be prudent (Demirci *et al*., 2002). Systemic metastasis to brain, lung, liver, or other distant sites occurs in 10-30% of patients with conjunctival melanoma (Constantopoulos *et al*., 2014). Tumor thickness greater than 2 mm and non-limbal location are associated with increased risk of metastasis and death (Yousem *et al*., 2010).

Kaposi's Sarcoma

Clinical Features: Kaposi's sarcoma is caused by human herpesvirus 8 (Gengler and Guillou, 2006). It tends to occur in immunosuppressed individuals, especially those suffering from HIV infection (Mashoto *et al*., 2013). The lesion has a reddish appearance similar to that of a pyogenic granuloma, subconjunctival hemorrhage or foreign-body granuloma.

Treatment and Prognosis: In selected cases where the lesion is nodular, it can be excised. In cases with diffuse Kaposi's sarcoma, external-beam radiotherapy with a dose of 8 Gy in a single fraction is given (Demirci *et al.*, 2002). Chemotherapy using interferon as well as active antiretroviral therapy have also been beneficial (Demirci *et al*., 2008).

Malignant Orbital Tumors in Adults (>18 Years of Age): Lymphoid Tumors (Ocular neoplasm Lymphoma)

Clinical Features: Ocular neoplasm lymphoma (OAL) represents the malignant end of the spectrum of Ocular neoplasm lymphoproliferative disease; which has reactive lymphoid hyperplasia (RLH) and RLH with atypia as its benign and intermediate forms, respectively. The overall incidence of systemic lymphoma is increasing but no corresponding information exists for OAL. Ocular neoplasm lymphomas can affect the orbit, lacrimal gland, eyelids or the conjunctiva. It most often present as a nontender, firm, subcutaneous mass in the anterior orbit; as a conjunctival salmon-patch infiltrate; or as an eyelid infiltration (Ruchman and Flanagan, 2013). However, in 30-40% of patients, systemic involvement is seen 5-10 years after diagnosis of the orbital lymphoma.

Most OALs are of the non-Hodgkin's stage IE (extranodal) low-grade B-cell variety (Ruchman and Flanagan, 2013). More superficial tumors of T-cell lineage, such as mycosis fungoides, can also occur in the periocular skin and typically cause a secondary ectropion of the lower eyelid. Ocular neoplasm lymphomas may be associated with systemic lymphoma; thus, a full systemic work-up is required for staging of the lymphoma and to look for other foci of lymph node involvement. Lymphoid lesions typically mold to structures such as the globe and bony orbit. In the differential diagnosis of orbit and eyelid OALs, dacryoadenitis, inflammation, metastasis and benign and malignant tumors must be considered (Mearkle *et al.*, 2016).Many lymphomas are thought to develop as a result of mistakes occurring during the normal lymphocyte response to infections or inflammation. There is increasing evidence of a role of chronic infection in OAL. Both Chlamydia Psittaci and Helicobacter Pylori have been identified to date in patients with OAL (Gengler and Guillou, 2006).

Histologic Features: The histopathologic spectrum for lymphoid tumors of the orbit ranges from benign reactive lymphoid hyperplasia to lymphoma. The histologic classification of lymphoma is beyond the scope of this review, but the Revised European-American Lymphoma (REAL) classification applies to tumors of the orbit. Most orbital lymphomas are of non-Hodgkin's B-cell type. OAL consists of five types of lymphoma, the most common of which is extranodal marginal zone (EMZL) or mucosa-associated lymphoid tissue (MALT) type followed by the follicular lymphoma. The other types including mantle cell

lymphoma, diffuse large B-cell lymphoma and lymphoplasmacytic lymphoma are occasionally seen in the orbit. T-cell lymphoma is rare in the orbit and usually of the natural killer cell variety.

Treatment and Prognosis: As for other extranodal forms of lymphoma, the treatment of Ocular neoplasm lymphoma depends on the stage and histologic classification. For isolated Ocular neoplasm lymphoma (stage IE) of low grade, external-beam radiation therapy is considered the standard therapy (Parkin *et al.*, 2005). For more widespread disease or for higher-grade lymphomas, systemic chemotherapy or a combination of chemotherapy and radiation therapy may be more appropriate (Croxatto and Font, 2018). Another alternative for stage IE low-grade lymphoma of the ocular adnexa, particularly low-grade B-cell follicular lymphoma or MALT lymphoma, may be monoclonal antibody therapy (Levitt *et al.*, 2015). The most commonly used antibody is CD20, rituximab, which leads to the destruction of B cells using mechanisms of complement- and antibody-mediated destruction as well as induction of apoptosis. These antibodies are most commonly used in combination with other agents, so their solitary effect is hard to assess. They seem to reduce but not eliminate lymphoma. Monoclonal antibody therapy with rituximab (Rituxan) or ibritumomab tiuxetan (Zevalin) is also an intriguing option given that it targets CD20-positive lymphomas and is given systemically, thus potentially decreasing the likelihood of systemic recurrence during the follow-up period (Ruchman and Flanagan, 2013). Monoclonal antibody therapy may also be less toxic than systemic chemotherapy and may be associated with less ocular toxicity than radiation therapy.

Using a 3-week course of doxycycline, there was a therapeutic effect in half of patients, presumably to eradicate the infection that underlies lymphomagenesis. Another study has shown effect in a few patients using the typical anti-*H. pylori* triple therapy (Demirci *et al.*, 2002). Controversy does exist as there are questions as to how antibiotic elimination of underlying infection could eradicate a genetic dysregulation. Fluorine 18 deoxyglucose (18FDG) PET proved to be useful in detecting systemic extranodal lymphomatous sites not detected in conventional imaging. Therefore, it may be used to evaluate systemic involvement in OAL patients (Levitt *et al.*, 2015).

Malignant Epithelial Lacrimal Gland Tumors

Clinical Features: Malignant epithelial lacrimal gland tumors account for approximately 15-25% of all lacrimal gland tumors (Cytryn *et al.*, 1997). Malignant tumors of the lacrimal gland include adenoid cystic carcinoma, pleomorphic adenocarcinoma and mucinous adenocarcinoma. Adenoid cystic carcinoma is the most common epithelial lacrimal gland malignancy but is still rare (Sepahdari *et al.*, 2010). Although adenoid cystic carcinoma is more common in adults, it can also occur in children. Pain due to perineural invasion is a common complaint. Neuroimaging studies reveal a round to oval mass with irregular margins and bony destruction (Figure 5).

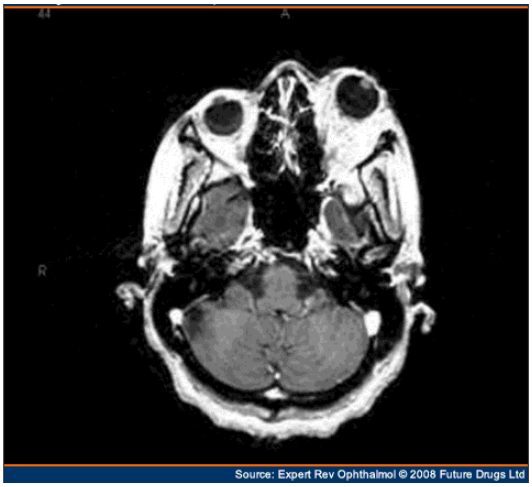

Figure 5: CT scan of a locally advanced adenoid cystic carcinoma of the lacrimal gland. Note that the lacrimal gland mass fills the orbit to the orbital apex.

Histologic Features: The histologic features of malignant epithelial lacrimal gland tumors differ with the tumor type. Adenoid cystic carcinoma presents most commonly with a cribriform (swiss cheese) pattern; the basaloid (solid), sclerosing, tubular and comedocarcinoma patterns are also seen (Vemuganti *et al.*, 2012). The basaloid variety has the worst prognosis (Cytryn *et al.*, 1997). Perineural invasion is commonly seen with adenoid cystic carcinoma.

Treatment and Prognosis: Treatment consists of complete surgical resection, if possible. Radical surgery in the form of orbital exenteration with removal of orbital bony walls and postoperative radiation therapy (in the form of external-beam radiotherapy or, less commonly, plaque brachytherapy) is often indicated (Jung *et al.*, 2007). Despite aggressive local therapy, a significant proportion of patients (>50% according to most series) develop metastatic disease; brain, bone and lung are the most common sites for distant metastasis. The mortality rate for adenoid cystic carcinoma of the lacrimal gland is greater than 50% at 5 years (Jung *et al.*, 2007).

Metastatic Orbital Tumors

Clinical Features: Like metastatic uveal tumors, most orbital metastases reach the orbit by the hematogenous route. Most metastatic orbital tumors are carcinomas and, in rare cases, melanomas and sarcomas occur. Breast, lung and prostate are the most common primary tumor sites; bronchial carcinoid, thyroid carcinoma and renal cell carcinoma are less common (Sepahdari *et al.*, 2010). Clinically, a metastatic orbital tumor presents with rapid onset of proptosis and displacement of the globe. Pain, diplopia and blurred vision can also be the presenting signs and symptoms. Disease is usually unilateral, but occasionally it is bilateral. Fibrotic tumors of the breast and stomach may cause enophthalmos. Neuro imaging studies, including CT and MRI scanning, reveal a well-circumscribed lesion in the case of orbital metastasis from lung cancer, carcinoid, melanoma, thyroid carcinoma or renal cell carcinoma.

Metastases from breast carcinoma often have a diffuse and ill-defined infiltrative appearance.

Treatment and Prognosis: Treatment of metastatic orbital tumors consists of an incisional biopsy if the diagnosis cannot be established on the basis of a previous history or imaging studies and if the location of the mass allows for a low-risk biopsy procedure. Systemic chemotherapy or local radiation therapy to the orbit can also be used for treatment of orbital metastases. In selected cases, hormonal therapy is also an option.

Secondary Tumors Extending to the Orbit from Adjacent Structures

Clinical Features: Secondary orbital tumors reach the orbit by direct extension from adjacent structures such as paranasal sinuses, nasal cavity, conjunctiva, eyelid or globe. Among the tumors that extend to the orbit are conjunctival SCC and conjunctival melanoma; eyelid tumors, including BCC, SCC, SGC and malignant melanoma of the eyelid; and intraocular tumors, including uveal melanoma, retinoblastoma and medullo epithelioma. Paranasal sinus carcinomas, nasopharyngeal carcinoma and angiofibroma, and sphenoid wing meningiomas can also invade the orbit.

Treatment and Prognosis: In many cases of orbital invasion from eyelid, conjunctival or intraocular tumors, orbital exenteration is indicated. The choice of an eyelid-sparing or eyelid-sacrificing technique depends on whether the eyelids are affected by tumor. On the other hand, in selected cases of orbital BCC, a globe-sparing orbital resection can be possible. Paranasal and nasopharyngeal carcinomas with orbital involvement require a multi-disciplinary approach involving specialists in head and neck surgery and neurosurgery. For extensive tumors not amenable to surgical resection, chemotherapy and external-beam radiation therapy can be used. In certain tumors such as sebaceous eyelid carcinoma or conjunctival malignant melanoma, additional lymph node resection should be considered when planning exenteration.

Malignant Orbital Tumors in Children (<18 years of age):

Rhabdomyosarcoma

Clinical Features: Rhabdomyosarcoma (RMS) is the most common primary malignant orbital tumor in children (Chirinos-Saldaña *et al*., 2013). The mean age at diagnosis is 8 years. RMS is occasionally congenital in onset. The tumor has a rapid onset, with proptosis and displacement of the globe. There may be eyelid edema and conjunctival chemosis resembling idiopathic orbital inflammation. Orbital imaging studies with contrast enhancement reveal a well-circumscribed and later diffuse mass. RMS originating from the nasopharynx can invade the orbit.

Histologic Features: Rhabdomyosarcoma is composed of poorly differentiated rhabdo myoblasts arranged in a loose myxomatous matrix. The characteristic tumor cell is the strap cell with cross striations. However, such cells are found in less than 60% of cases. The embryonal form is the most common form of RMS and the alveolar form is the most malignant. The pleomorphic form is least common and occurs in adults. The botryoid form is associated with a mucous membrane such as the conjunctiva. Alveolar RMS is less common, tends to arise in the inferior orbit, has a characteristic translocation (t [2;13]) and tends to have a poorer prognosis (Cytryn *et al*., 1997).

Immunohistochemistry aids in the diagnosis and determining the subtype of RMS. Numerous immunohistochemical markers including desmin, vimentin, muscle-specific actions, myoglobin, myogenin, myoD1, and caveolin-3 can identify the skeletal muscle-specific (SMA) expression in a RMS tumor. Antibodies against desmin show the greatest specificity and retain positive reaction in even poorly differentiated rhabdomyoblasts (Valvassori *et al*., 2019).

Treatment and Prognosis: A full metastatic evaluation should be included to rule out systemic involvement. The current Intergroup Rhabdomyosarcoma Study (IRS) treatment protocols, based on group, stage, histology and patient age, contribute to the risk and treatment stratification necessary to optimize outcome (Jung *et al*., 2007). A biopsy is necessary to establish the diagnosis. During the biopsy procedure, it is wise to remove as much tumor as possible without damaging vital orbital structures. Combined chemotherapy and irradiation are the mainstays of therapy for orbital RMS. Isolated orbital involvement carries the best prognosis of all primary RMS locations, with an overall survival rate of 96% (Sepahdari *et al.*, 2010). Children who present between ages 1 and 10 years have a more favorable prognosis than infants and adults. Of the radiotherapy options, stereotactic radiotherapy with intensity-modulated radiotherapy (IMRT), proton beam radiation therapy and brachytherapy may produce similar results with fewer sequelae compared with the standard EBRT (Cytryn *et al*., 1997). Standard EBRT leads to several complications including cataract, impaired vision, orbital hypoplasia and asymmetry, dry eye, and ptosis/enophthalmos in many patients.

Granulocytic Sarcoma (Chloroma)

Clinical Features: Soft tissue infiltration by myelogenous leukemia (a condition known as granulocytic sarcoma or chloroma) usually occurs in young children (Sepahdari *et al*., 2010). Systemic disease is usually present before the onset of orbital disease. However, in rare cases the orbital lesion is the first manifestation of myelogenous leukemia. Clinically, there is rapid onset with proptosis and displacement of the globe, alongside a palpable anterior orbital mass.

CONCLUSION

Early detection of neoplastic disease of the eye through judicious use of sentinel node biopsy and newer computerized imaging modalities such as PET by the Optometrist may make an overall difference in the survival of patients with aggressive tumors of the ocular adnexa. Optometrists who are specialists in occulastry/occuloplasty form part of the team. Expertise in eyelid and periocular reconstruction by the oculoplastic surgeon in the multidisciplinary management of eyelid, conjunctival and orbital cancers will allow for globe preservation and the use of adjuvant postoperative radiation therapy in lieu of radical surgery. Early detection/diagnosis and professional referral

by the Optometrist is key in the multidisciplinary management of neoplastic disorders of visual apparatus.

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