EYELID TUMORS: A REVIEW

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Abstract: *Tumors of the eyelid are frequently benign in nature. The commonest benign tumors are cystic in nature while the commonest malignant tumors are epithelial in origin. An eyelid tumor generally presents at an early stage as a visible eyelid mass, and wide excision with primary lid reconstruction is curative. Those presenting with extensive lesions require careful planning for excisional surgery followed by lid reconstruction with grafts or flaps. Additionally, radiotherapy maybe necessary in bony involvement. Extensive orbital extension necessitates exenteration.*

The eyelid is composed of two lamellae-the anterior lamella comprising the skin and the orbicularis, and the posterior lamella comprising the tarsus and the palpebral conjunctiva. The eyelid margin is a composite structure on its own, containing hair follicles and the glands associated with it, openings of meibomian glands, and the transition from the tarsal conjunctiva to the skin of the lid. All these structures present within the lid can give rise to neoplastic lesions of different varieties. Commonest are the ones arising from the epithelial layer of the lids. Herein, we discuss the common benign and malignant lesions of the eyelid (Table 1).

CYSTIC TUMORS OF THE EYELID

Various cystic lesions arising in the skin of the eyelids simulate neoplasms. These include eccrine hidrocystoma, apocrine hidrocystoma, sebaceous cyst and epidermoid cyst. Eccrine hidrocystoma is a retention cyst of the eccrine sweat glands. It appears as a clear cyst located near the eyelid margin (Figure 1A). Apocrine hidrocystoma is a retention cyst of the apocrine glands most commonly occurring near the eyelid margin. It arises from the glands of Moll and has a bluish color. In contrast to eccrine hidrocystoma which can be multiple, apocrine hidrocystoma is usually solitary. Sebaceous cyst is a retention cyst of the sebaceous glands, either meibomian glands or Zeis glands. It appears as a yellow, opaque lesion near the eyelid margin or in the periocular skin (Figure 1B). Epidermoid cyst is a retention cyst caused by obstruction of the orifices of the pilosebaceous units, which clinically resembles a sebaceous cyst. However, the cyst largely contains desquamated keratin. Management of these cysts can be just observation or surgical excision. Carbon dioxide laser-assisted or radiofrequency-assisted vaporization may also be performed.

EYELID SQUAMOUS PAPILLOMA

Squamous papilloma is histopathologically characterized by benign hyperplasia of squamous epithelium. It is one of the most common eyelid lesions and unlike the conjunctival papilloma, no strong association with human papilloma virus has been found. Seen in elderly individuals, eyelid papillomas can be sessile or pedunculated, solitary or multiple with smooth or convoluted surface (Figure 2A). Management of these lesions can be just observation or shave excision. Carbon dioxide laser-assisted or radiofrequency-assisted vaporization may also be performed.

EYELID SEBORRHEIC KERATOSIS

Seborrheic keratosis generally occurs in the periocular region of older individuals. The lesion appears as a minimally elevated tan to brown plaque which is frequently solitary (Figure 2B). However, the sudden appearance of multiple lesions may indicate the presence of an internal malignancy, more specifically gastrointestinal adenocarcinomas. This is called the "Sign of Leser-Trelat". Treatment is observation or

Figure 1: *Benign tumors of the epidermis (A) A transparent, cystic eccrine hidrocystoma located near the eyelid margin (B) A typical sebaceous cyst*

Figure 2: *Benign tumors of the epidermis (A) A single pedunculated papilloma with a convoluted surface (B) A tan colored plaque representing an actinic keratosis*

Figure 3: *Pre-malignant periocular skin lesions (A) Xeroderma pigmentosum (B) A geographic pattern of pigmentation representing a sebaceous nevus*

Table 1: Benign and Malignant Tumors of the Eyelid			
Tumors of the eyelid	**Benign**	**Pre-Malignant**	**Malignant**
1. Cystic tumors	Eyelid eccrine hidrocystoma Eyelid apocrine hidrocystoma Eyelid sebaceous cyst Eyelid epidermal inclusion cyst		
2. Tumors of the epidermis	Eyelid squamous papilloma Eyelid seborrheic keratitis Eyelid inverted follicular keratitis Eyelid keratoacanthoma	Eyelid actinic keratosis Xeroderma Pigmentosum Sebaceous Nevus	Eyelid squamous cell carcinoma Eyelid basal cell carcinoma
3. Sebaceous gland tumors	Eyelid sebaceous adenoma		Eyelid sebaceous carcinoma
4. Sweat gland tumors	Eyelid syringoma Eyelid eccrine hidradenoma		Eyelid sweat gland adenocarcinoma
5. Hair follicle tumors	Eyelid trichoepithelioma Eyelid trichofolliculoma Eyelid trichoadenoma Eyelid tricholemmoma		Eyelid trichilemmal carcinoma
6. Melanocytic tumors	Eyelid melanocytic nevus Oculodermal melanocytosis	Eyelid lentigo maligna	Eyelid malignant melanoma
7. Neural tumors	Eyelid neurofibroma Eyelid schwannoma		Eyelid Merkel cell carcinoma
8. Vascular tumors	Eyelid congenital capillary hemangioma Eyelid acquired capillary hemangioma Eyelid varix Eyelid lymphangioma		Eyelid Kaposi's sarcoma Eyelid angiosarcoma Eyelid glomus tumor
9. Histiocytic and fibrous tumors	Eyelid xanthelasma and xanthoma Eyelid xanthogranuloma Eyelid angiofibroma		
10. Lymphoid tumors	Eyelid eccrine hidradenoma		Eyelid lymphoma
11. Tumors of the lacrimal drainage system	Eyelid trichoepithelioma		Lacrimal gland carcinoma Lacrimal sac melanoma

shave excision. Carbon dioxide laser-assisted or radiofrequency-assisted vaporization may also be performed.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is an autosomal-recessive disorder in which there is a defect in DNA-repairing enzymes. Such patients are extremely sensitive to ultraviolet radiation from the sun that can predispose them to a variety of cancers, including tumors of the eyelid and conjunctiva. The skin of the affected individuals shows variegated pigmentation, scaling and telangiectasia (Figure 3A). Multiple tumors develop by the end of 1st decade including squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and sarcomas. Management mainly includes protection from sunlight with use of topical sunscreen applications, protective clothing, ultraviolet blocking spectacles, and surgical excision of small premalignant and malignant skin lesions.

SEBACEOUS NEVUS

Sebaceous nevus can be an isolated lesion in the eyelid area, or a part of a systemic syndrome, organoid nevus syndrome. Organoid nevus syndrome primarily has neurologic manifestations with arachnoid cysts and cerebral atrophy leading to seizures and mental retardation. The ocular findings include large pigmented patch (tan to brown) in the scalp, eyelids, face and retroauricular area and conjunctival choristoma (Figure 3B). This cutaneous lesion can frequently give rise to BCC, which is reported in approximately 20% of the patients. Regarding management, small lesions can be excised. Lesions which are too extensive for excision can be simply observed. Any tumor arising within the lesion should be completely excised.

EYELID SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) accounts for 5% to 10% of periocular cutaneous tumors, and is the second most common cancer of the eyelids. These tumors can arise either de novo or from precursor lesions, including actinic keratosis, Bowen's disease, xeroderma pigmentosa or albinism. Patients with xeroderma pigmentosa tend to be younger, have multiple and recurrent cutaneous lesions in the eyelids and other parts of the body. The lower eyelid is the most common periocular site to be involved. SCC in the eyelid tends to appear sessile or elevated, erythematous with indurated borders and with a scaly surface (Figures 4A-B).

Figure 4: *Squamous cell carcinoma (SCC) of the eyelid (A) presenting as a sessile necrotic lesion (B) and as a nodular lesion with conjunctival extension*

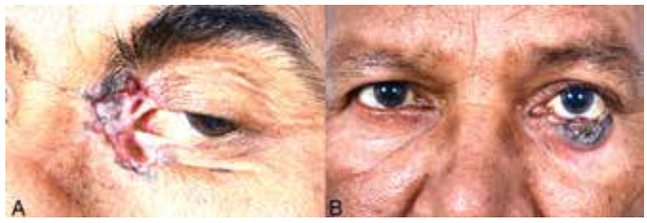

Figure 5: *Basal cell carcinoma (BCC) of the eyelid (A) Typical location of an eyelid BCC causing ectropion of the lower lid (B) An early nodular pigmented BCC of the upper lid*

The lesions frequently ulcerate, become friable, and tend to bleed on touch. Sometimes the central part of a necrotic lesion may develop a secondary infection. SCC of eyelid shows neurotropism and regional lymph node metastasis. Histopathologically, the tumor consists of nests of squamous epithelial cells arising from the epidermis and extending into the dermis. These cells with eosinophilic cytoplasm can also contain keratin pearls.

SCC of the eyelid is known to be aggressive with prognosis correlating with local recurrence and metastatic rate. Treatment options include excision biopsy in conjunction with histological monitoring of tumor margins, radiation, cryotherapy, intralesional chemotherapy and intralesional interferon. Radiation may be especially useful in cases with perineural invasion as an adjunctive therapy. Exenteration is reserved for cases where there is an evidence of extensive orbital invasion.

EYELID BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is the most common malignant tumor of the periocular skin. It most commonly arises from the lower lid (65%) followed by medial canthus (15%) and upper eyelid (15%). Exposure to UV radiation is the most important risk factor. BCC is associated with genetic syndromes including Gorlin-Goltz syndrome and xeroderma pigmentosa. It characteristically presents as a well-circumscribed, pearly, waxy or translucent tumor with telangiectasia visible near the border of the lesion. Most common clinical types of BCC are nodular and nodulo-ulcerative (Figures 5A-B). Other varieties include pigmented, cystic, superficial and morpheaform BCC. Histopathologically, the tumor cells consist of nests of well-differentiated basal cells arranged in a palisading pattern. Although BCC of the eyelid is known to have a gradual clinical course with a low incidence of metastasis and mortality, advanced BCC can invade the orbit, nasal cavity and sinuses.

Complete surgical excision under frozen section control offers a long-term cure in early lesions. Cryotherapy has also been tried in smaller lesions with comparable outcome. Immunomodulator agents, as a cure for small periocular BCC, have gained popularity in the recent past. Topical application of 5% Imiquimod offers an excellent alternative treatment for small to medium sized periocular BCC. Although some authors have advocated the use of radiotherapy in small lesions, it is now generally offered in patients as a palliative treatment in recurrent lesions or in advanced BCC with orbital, intranasal or intracranial extension. Vismodegib is a new FDA approved treatment option for metastatic and locally advanced BCCs that are not amenable to surgery or radiation. Vismodegib, given orally at a dose of 150 mg once a day, inhibits the Hedgehog signalling pathway, which is abnormally up regulated in more than 90% of BCC.

EYELID SEBACEOUS CARCINOMA

Sebaceous gland carcinoma of the ocular adnexa can arise from the meibomian glands, Zeis glands of the cilia, the glands of the eyebrows, the caruncle, and also the glands of the fine hair follicles on the skin of the eyelid. Periocular region accounts for 75% of all sebaceous gland carcinoma, although extra-ocular sites are also well-known; this is due to the fact that there is an abundance of sebaceous glands in this area. In the west, sebaceous gland carcinoma has been reported to account for approximately 2–7% of all eyelid malignancies. In contrast, several studies from India, China and Japan have reported that sebaceous gland carcinoma accounts for up to 30% of malignant eyelid neoplasms, and is the second most common malignant eyelid neoplasm in these regions after basal cell carcinoma.

Eyelid sebaceous gland carcinoma presents either as a solitary nodule or diffuse lid thickening, in which case it may often be misinterpreted as chronic blepharitis (Figures 6A-D). The latter presentation of sebaceous gland carcinoma often leads to a delay in accurate diagnosis and treatment, often leading to an unfavorable prognosis. The tumor typically causes distortion of the posterior lid margin, blockage of meibomian gland orifices, loss of cilia, with surrounding telangiectasia and sometimes ulceration in advanced cases. Upto 35% of the patients can have a pagetoid spread on histopathology, and it may involve both eyelids and conjunctival epithelium.

Etiological factors leading to sebaceous gland carcinoma are not well-established. Sebaceous gland carcinoma occurs in patients with Muir– Torre syndrome, a rare autosomal dominant disorder characterized by neoplasms of the sebaceous glands and visceral malignancies that is caused by mutation of DNA mismatch repair genes, leading to the propagation of genetic defects within replicating cells and predisposition to tumor formation. Histopathologically, the tumor consists of malignant proliferation of sebaceous cells with vacuolated cytoplasm owing to the presence of lipid.

Standard treatment for sebaceous gland carcinoma of eyelid consists of wide local excision with frozen section or Mohs microsurgery. When a pagetoid conjunctival spread is suspected, several small map biopsies are done to determine the extent of the lesion, followed by a definitive surgical planning. Orbital Exenteration is considered when there is spread into the anterior orbit. Radical neck dissection is necessary in patients with locoregional metastases as in other malignant tumors of the eyelid. Alternative treatments include cryotherapy, topical or systemic chemotherapy and radiotherapy. Cryotherapy is a useful adjunctive treatment for epibulbar and pagetoid extension of sebaceous gland carcinoma. Topical Mitomycin C has been tried for eyelid sebaceous gland carcinoma with or without pagetoid spread with variable success. Systemic chemotherapy as a neoadjuvant treatment in advanced periocular sebaceous gland carcinoma

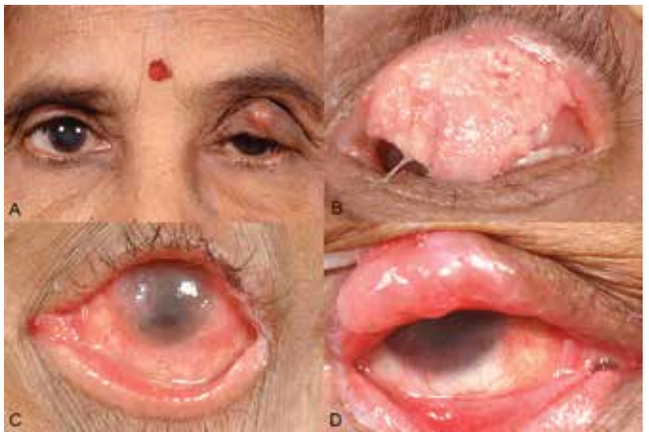

Figure 6: *Sebaceous carcinoma of the eyelid (A) Chalazion-like presentation of an eyelid sebaceous gland carcinoma (SGC) (B) Same patient on lid eversion shows an extensive tumor (C) Diffuse conjunctival involvement by SGC presenting as chronic conjunctivitis (D) Typical presentation of SGC with diffuse thickening of the lid margin, erythema, and loss of cilia*

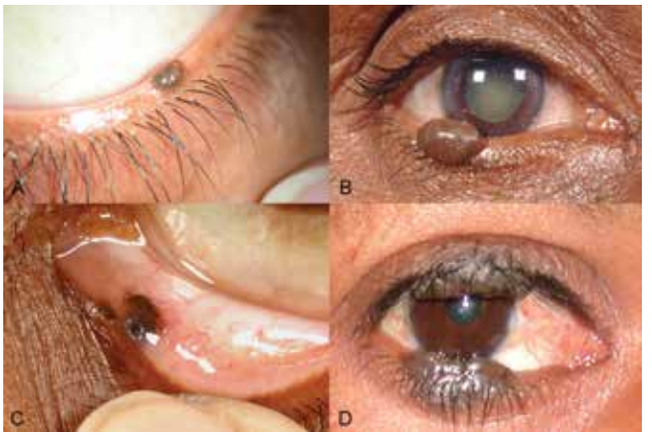

Figure 7: *Melanocytic tumors of the eyelid: different presentations of a nevus (A) A small, flat marginal nevus (B) A hypertrophied marginal nevus (C) An atypical peripunctal location of an eyelid nevus (D) A "kissing" nevus*

is evolving. Although sebaceous gland carcinoma is considered to be radiosensitive, radiation therapy for this has been described in very few short case series, mostly as an alternative to surgical treatment in patients who may be poor surgical candidates.

EYELID MELANOCYTIC NEVUS

Melanocytic nevus of the eyelid, like any other nevus, comprises of melanocytes derived from the neural crest that migrate to the skin during embryonic development. A nevus can be acquired or congenital. Depending on the location, nevi are divided into junctional, compound, and intradermal types. In general, childhood nevi are junctional and in adulthood, there is a tendency towards migration into the dermis. The clinical features vary with patient age and stage of the disease. The nevus can vary in size, location and pigmentation (Figures 7A-C). Completely amelanotic nevi commonly occur in the eyelids. A variant of congenital nevus is the "kissing" nevus of the upper and lower lid which occurs due to the formation of the nevus before the lid separation during embryological development (Figure 7D). Management is generally observation. Surgical excision maybe performed in those causing cosmetic blemish.

OCULODERMAL MELANOCYTOSIS

Oculodermal melanocytosis is a bluish-black pigmentation of the periocular skin, uveal tract, and sometimes ipsilateral orbital soft tissues, ipsilateral pinna, ipsilateral meninges, and ipsilateral hard palate (Figures 8A-B). The pigmentation is congenital, and the eyelid pigmentation is known as the nevus of Ota. It tends to follow the distribution of the first and second divisions of the trigeminal nerves. Bilaterality is seen in about 10% of cases. In the uveal tract, this condition predisposes to formation of uveal melanoma. Malignant transformation of the eyelid component into cutaneous melanoma is rare. Histopathologically, nevus of Ota is characterized by increase in the number of scattered dendritic melanocytes in the dermis. Management is generally close observation.

EYELID LENTIGO MALIGNA

Lentigo maligna or melanotic freckle of Hutchinson is an acquired pigmentation that usually occurs on sun-exposed areas. It can rarely involve the eyelid as a small localized lesion. It is rare in darkly pigmented individuals. Clinically, the lesion appears as a flat, tan to brown pigmentation with well-demarcated borders. It enlarges slowly over years. Lentigo maligna is the precursor lesion of lentigo maligna melanoma. A melanoma secondary to lentigo maligna is also flat or minimally elevated in the early stages. Management is by wide surgical resection.

EYELID MALIGNANT MELANOMA

Periocular malignant melanoma is a rare condition, accounting for less than 1% of malignant eyelid neoplasms. It can occur in the eyelid as a primary lesion or as an extension of a conjunctival melanoma, or rarely, as a metastasis from a distant primary (Figures 8C-D). Majority of patients present in their sixth and seventh decade. The most common type in the periocular area is Lentigo maligna melanoma, followed by superficial spreading melanoma and nodular melanoma. Lentigo maligna melanoma and superficial spreading melanoma are characterized by radial growth confined to the epidermis in the early stages, followed by invasion of subepidermal structures. In contrast, nodular melanoma exhibits early invasion of the subepidermal tissue.

Patients with malignant melanoma most commonly present with a sudden change in the appearance of a preexisting nevus. Increase in size and pigmentation, elevation, tenderness, and ulceration point towards malignant transformation. Lower lid is the most common site for eyelid melanoma, followed by upper lid, lateral canthus, and medial canthus. Histopathologically, the malignant cells are of three types- spindle cells, epithelioid cells, or nevus-like cells. Wide local excision is the treatment of choice for malignant melanoma. Advanced cases with orbital involvement may require orbital exenteration. The patient should be checked for preauricular and submandibular lymphadenopathy.

EYELID CAPILLARY HEMANGIOMA

Capillary hemangioma can be congenital (infantile capillary hemangiomas or strawberry hemangiomas) or acquired. Acquired capillary hemangiomas are very tiny lesions which are red-blue in color

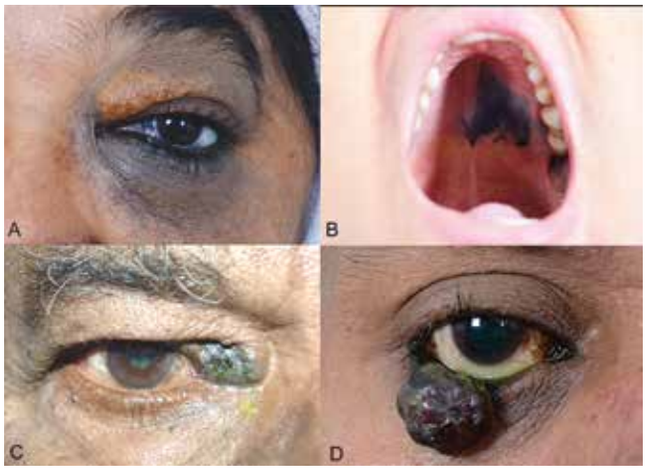

Figure 8: *Melanocytic tumors of the eyelid (A) Oculodermal melanocytosis with slate-grey pigmentation of the periocular skin and episclera (B) Ipsilateral palatal pigmentation in the same patient (C) An eyelid malignant melanoma with caruncular extension (D) A large eyelid malignant melanoma secondary to extension from the conjunctiva*

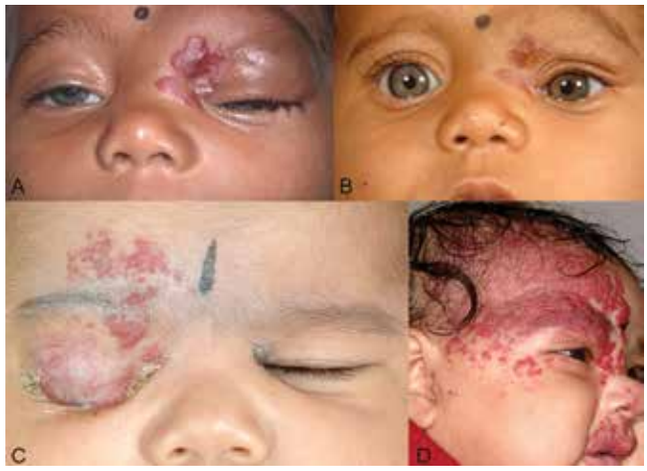

Figure 9: *Capillary hemangioma of infancy (A) Large periocular capillary hemangioma causing ptosis (B) Same patient after treatment with intralesional steroids (C) Complete ptosis secondary to a large capillary hemangioma (D) Extensive hemangioma involving the ipsilateral scalp, periocular and perioral region*

(cherry hemangiomas) seen in elderly individuals. These generally do not require any treatment. Congenital capillary hemangioma develops either at birth or within the first year of life. It can be located superficially (anterior to the orbital septum), deep (posterior to the orbital septum), or both. Regarding its etiopathogenesis, due to the similar immunohistochemical characteristics with the placenta, it is believed that infantile hemangiomas could be of placental origin.

Eyelid capillary hemangiomas are not present at birth, but develop in the first few months of life and continue to enlarge over the first 6-12 months after the first year (proliferative phase), with 90% resolution occurring within 8 years of life (involutional phase). Periocular capillary hemangioma of infancy may be seen in association with Kasabach-Merritt syndrome, which is characterized by large visceral hemangiomas, platelet entrapment and thrombocytopenia. Some of the superficial hemangiomas can lie in the subcutaneous tissues with little or no involvement of the epidermis (Figures 9A-D). The skin overlying the lesion has a bluish hue, and the lesion becomes more apparent with crying or straining.

Lesions greater than 1 cm in diameter are more likely to cause complications, with an incidence of amblyopia upto 60%. The amblyopia can either be from pupil obstruction or from refractive errors induced by the compression of the globe by the tumor. Periocular capillary hemangioma can also cause strabismus secondary to tumor compressing the recti muscles or amblyopia.

Most tumors can be managed by observation, although those causing amblyopia should be treated with refraction and occlusive patching. Oral use or local injection of corticosteroids can hasten regression of the lesion. Oral prednisolone 2 to 4 mg/kg/day for 2-4 weeks is administered under the supervision of a pediatrician. The major risks include adrenal suppression and growth retardation. Intralesional corticosteroids are administered as a combination of triamcinolone 1 mL (40 mg/mL) and dexamethasone 1 mL (4 mg/mL). Interferon α-2a upto 3 million units/m2 of body surface area can be given as daily subcutaneous injections for vision-threatening hemangiomas to cause complete regression of the lesions. Propranolol is a non-selective beta blocker that can be used systemically for eyelid capillary hemangiomas with high efficacy. The recommended dosage of oral propranolol is 2 to 3 mg/kg/day until regression and additionally for a month to prevent recurrence. Surgical treatment is rarely necessary, but can be considered in those with visual symptoms not responding to pharmacologic modalities.

EYELID KAPOSI'S SARCOMA

Kaposi's sarcoma is an endothelial cell malignancy seen more commonly in immunosuppressed individuals. Kaposi's sarcoma of the eyelid is generally seen in association with AIDS. The lesion presents as a red, purple or blue flat subcutaneous nodule (Figures 10A-B). It is frequently well-circumscribed, but can be diffuse and large. Histopathologically, it is composed of proliferating groups of endothelial cells that contain blood-filled spaces. Management is generally for palliative purpose. When the lesion is diffuse, chemotherapy is more effective than radiation. For smaller lesions, low-dose radiotherapy (15–20 Gy) in fractionated doses is curative.

EYELID HISTIOCYTIC TUMORS

Xanthelasma is a common, benign subcutaneous, minimally elevated eyelid lesion. When it is nodular, it is called a xanthoma. Xanthelasma tends to be bilateral and is more common in the elderly. It occurs in 1-3% of individuals and more frequently in women. Half of the patients with xanthelasma are normolipemic while the other half has essential or secondary hyperlipidemia. It appears as a yellow, placoid lesion that affects the medial aspect of the eyelids. It is frequently bilateral and symmetrical. Microscopically, xanthelasma and xanthoma is composed of foamy histiocytes infiltrating the dermis. Surgical excision should be considered for larger lesions causing cosmetic blemish. Topical application of 35% trichloroacetic acid is proven to be effective. Carbon dioxide laser-assisted or radiofrequency-assisted vapourization may also be performed.

Juvenile xanthogranuloma is an idiopathic granulomatous inflammation that affects older children. It appears as an orange nodule which generally regresses on its own. It is typically composed of histiocytes, lymphocytes, mononuclear cells, eosinophils, and Touton giant cells. Management is generally by observation.

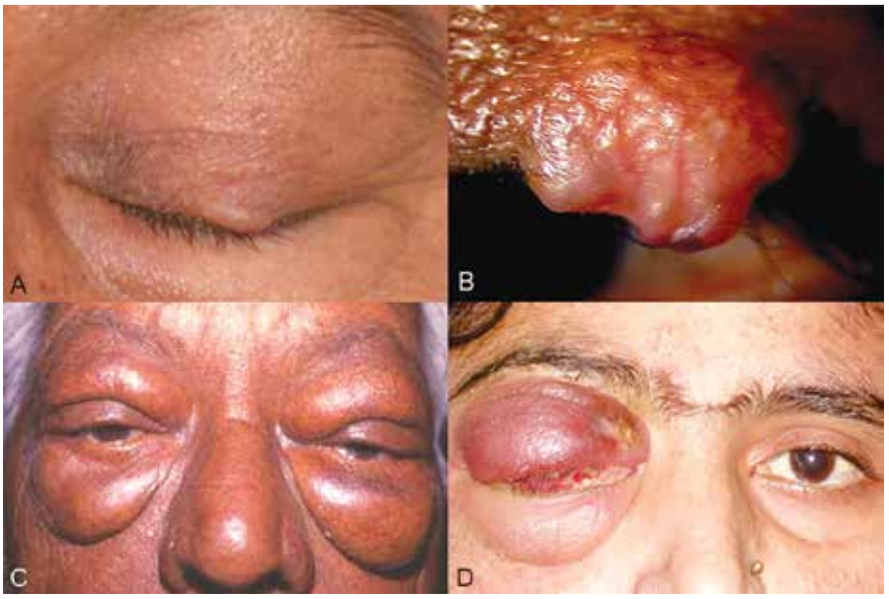

Figure 10: *Other rare tumors of the lid (A) Eyelid Kaposi's sarcoma presenting as a small mass in the upper lid (B) Rapid growth of the tumor in the same patient with a reddish-blue hue to the tumor (C) Typical appearance of a xanthogranulomatous tumor with bilateral lid involvement imparting the skin a yellowish color (D) Eyelid lymphoma with orbital extension*

Systemic or intralesional corticosteroids can be effective in refractory cases. Surgical excision may be performed if the lesion fails to respond to corticosteroids. The adult form of xanthogranuloma can occur as a solitary lesion often in patients with severe asthma (Figure 10C).

EYELID LYMPHOMA

Primary eyelid lymphomas are extremely rare. Like orbital lymphomas, eyelid lymphomas are also of B-cell type. It presents as a painless subcutaneous mass (Figure 10D). Rarely, cutaneous T-cell lymphoma (mycosis fungoides) may be seen, and this generally occurs in immunocompromised individuals. It appears as an eczema or in the form of ulceration, causing cutaneous inflammation with induration. The lesion can be solitary or multiple. Localized lesions can be controlled with radiation therapy, whereas systemic disease is treated with chemotherapy.

In conclusion, the commonest lesions affecting the eyelid are benign in nature. Primary malignant tumors affecting the lid are frequently epithelial in origin, and metastatic eyelid tumors are extremely rare. Eyelid tumors generally present in early stages, and wide excision with primary lid reconstruction is curative. Those presenting with extensive lesions require careful planning for excisional surgery followed by lid reconstruction with grafts or flaps. Additionally, radiotherapy maybe necessary in bony involvement. Orbital extension of these tumors requires exenteration.

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