Clinical Ophthalmic Oncology

Eyelid and Conjunctival Tumors

Jacob Pe'er
Arun D. Singh
Bertil E. Damato
Editors

Third Edition

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Preface

Ophthalmic tumors are rare and diverse so that their diagnosis can be quite complex. Treatment usually requires special expertise and equipment and, in many instances, is controversial. The field is advancing rapidly, because of accelerating progress in tumor biology, pharmacology, and instrumentation. Increasingly, the care of patients with an ocular or adnexal tumor is provided by a multidisciplinary team, consisting of ocular oncologists, general oncologists, radiotherapists, pathologists, psychologists, and other specialists.

For all these reasons, we felt that there was a need for the new edition of the textbook providing a balanced view of current clinical practice. Although each section of *Clinical Ophthalmic Oncology, 3rd Edition* now represents a standalone volume, each chapter has a similar layout with boxes that highlight the key features, tables that provide comparison, and flow diagrams that outline therapeutic approaches.

The enormous task of editing a multi-author, multivolume textbook could not have been possible without the support and guidance by the staff at Springer: Caitlin Prim, Melanie Zerah, ArulRonika Pathinathan, and Karthik Rajasekar. Michael D. Sova kept the pressure to meet the production deadlines.

It is our sincere hope that our efforts will meet high expectation of the readers.

Jerusalem, Israel — Jacob Pe'er, MD
Oxford, UK — Bertil E. Damato, MD, PhD, FRCOphth
Cleveland, OH, USA — Arun D. Singh, MD

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To my wife, Edith, and my children, Liron, Neta, and Doron, for years of support and patience.

Jacob Pe'er, MD

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Bertil E. Damato, MD, PhD, FRCOphth

To my parents who educated me beyond their means, my wife, Annapurna, and my children, Nakul and Rahul, who make all my efforts worthwhile.

Arun D. Singh, MD

Contents

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1 Eyelid Tumors: Examination Techniques

Catherine J. Hwang and Julian D. Perry

Introduction

Neoplasia may develop within any eyelid structure. Examination of the eyelid is thought to be relatively straightforward, given its anterior location and the ability to visualize its anterior and posterior surfaces. However, examination including structure and function is critical to determine the layers of the eyelid involved and if there might be extension posteriorly into the orbit or medially into the lacrimal system. The examination of an eyelid tumor determines the need for any ancillary tests and the surgical plan.

History

The history begins with a description of the symptoms: severity, onset, and rate of progression. A targeted review of systems reveals additional clues to the etiology.

The authors of the chapter would like to thank Dr. Bryan R. Costin for his contribution towards previous edition of this chapter.

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Presenting Symptoms

Eyelid neoplasia present with a limited spectrum of symptoms (Box 1.1). Most often, patients notice an abnormal eyelid appearance or asymmetry compared to the contralateral eyelid. The eyelid may harbor a distinct lesion, displaying elevation, ulceration, crusting, bleeding, altered pigmentation, telangiectasia, or other visible cutaneous or conjunctival changes. The patient may complain of loss of eyelashes or an irregularity along the eyelid margin.

Box 1.1 Symptoms of Eyelid Neoplasia

- Sensory: tenderness, itching, visual changes
- Motor: ptosis, lagophthalmos
- Structural: visible or palpable lesion, change in symmetry
- Functional: keratopathy or tearing
- Secondary: pigmentation, lymphadenopathy

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Eyelid neoplasia may produce symptoms that occur with or without visible structural changes. Sensory symptoms such as pain, tenderness, itching, or vision symptoms due to keratopathy, induced astigmatism, or obstruction of vision may develop. Motor symptoms, such as blepharoptosis or lagophthalmos, may develop owing to involvement of the eyelid retractors and protractors or indirectly from a mass effect. Functional symptoms develop from mechanical keratoconjunctivitis, exposure keratopathy, or decreased lacrimal outflow.

Rate of Onset

Rapidity and progression help characterize the pathology. Most symptoms from eyelid tumors develop over weeks to months, but associated hemorrhage, infection, and inflammation may be acute. Both benign (e.g., angiomas, papillomas) and malignant (e.g., cutaneous malignancies, metastases) eyelid tumors can produce hemorrhage. Any eyelid tumor that blocks lacrimal outflow or causes diminished cutaneous integrity can result in infection. Eyelid tumors may also be associated with a significant inflammatory reactions.

Past Medical History

Because the majority of eyelid neoplasms are epidermal in origin, the past medical history should focus on risk factors for epidermal malignancy. Information should be obtained regarding family history of cutaneous malignancy, skin type, freckle density, eye color, hair color, and prior history of skin cancer. Patients of Celtic or Scandinavian descent with blonde or red hair, blue eyes, and fair skin carry a greater risk for cutaneous malignancy [1, 2]. The history should also include immunosuppression, tobacco use, prior radiotherapy, sun exposure, and similar growths elsewhere on the skin.

Examination

The physical examination of an adult with suspected eyelid neoplasia does not end with direct visualization of the lesion. It should include a comprehensive inspection of the eyelid, ocular adnexa and orbit, eye, and other cutaneous lesions described in the history. Underlying conditions that may make reconstruction more challenging should be noted, including prominent globe, midface ptosis, hypoplastic orbital rim, lack of cutaneous or tissue redundancy, previous scarring from cutaneous malignancy repair or other surgery, asymmetry, lymph node enlargement, lagophthalmos, trichiasis, dry eye syndrome, and blepharitis.

Eyelid Examination

The patient should point out smaller lesions to the examiner using a hand mirror. The entire face should be evaluated to note Fitzpatrick skin type and any other cutaneous lesions. The eyelid examination should describe the appearance of the lesion, any associated anatomical deformities, and the results of palpation. The dimensions should be measured using a ruler or slit lamp beam. The eyelid examination should focus particularly on signs of malignancy, including telangiectasia, nodularity, pearly

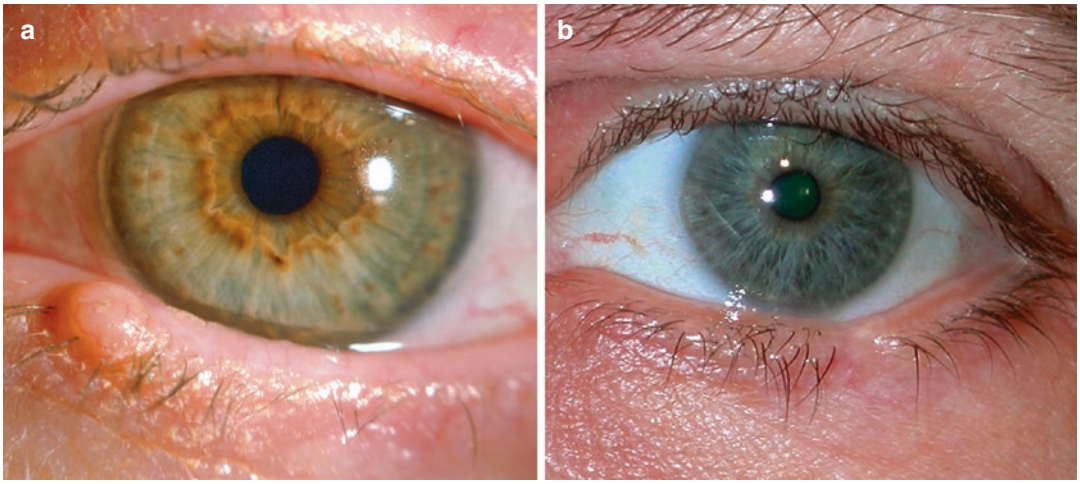

Fig. 1.1 Photograph of lower eyelid shows a benign eyelid nodule without loss of lashes (**a**) and loss of eyelid tissue with cilia loss secondary to a malignant tumor (**b**)

translucency, ulceration, bleeding, crusting, irregularity of the eyelid margin, meibomian gland effacement, misdirection of lashes or trichiasis, and loss of cilia (Fig.1.1; Box 1.2). Palpation results should describe the mobility of the lesion, as well as any fluctuance or associated tenderness. Color changes and irregularities should be noted.

Box 1.2 Signs of Malignant Eyelid Tumor

- Telangiectasia
- Nodularity, pearly translucency
- Ulceration, bleeding, crusting, margin notch
- Misdirection of lashes or trichiasis
- Loss of cilia
- Effacement of meibomian gland orifice

Function of the eyelid including levator excursion, orbicularis function, lagophthalmos, and lid lag in downgaze should be measured and noted. Horizontal eyelid laxity, blepharoptosis, cutaneous insufficiency, and other preexisting eyelid malpositions, scarring, and conditions should be noted, as they may challenge repair and will affect the reconstruction design. In addition, patients that relate these preoperative conditions to eyelid tumor surgery in the follow-up period can be reminded of the preoperative findings.

Ocular Adnexal Examination

Eyelid tumors may spread directly to the lacrimal gland, orbit, or lacrimal outflow apparatus. Conversely, primary tumors of these areas may occasionally present with only eyelid signs and symptoms. The structure and function of the orbit and ocular adnexal tissues in proximity to the

lesion should be evaluated. The examiner should palpate for preauricular, submandibular, cervical and supraclavicular adenopathy. Cranial nerves V and VII should be tested carefully to assess for involvement and possible perineural spread of an eyelid malignancy.

Eye Examination

The ocular examination should focus on detecting findings caused by, or associated with, the eyelid lesion. Slit lamp biomicroscopy may reveal signs of mechanical or exposure keratoconjunctivitis, or it may reveal signs of conjunctival spread of sebaceous cell carcinoma or cutaneous malignancy. During the evaluation of a pigmented eyelid lesion, the sclera and episclera should be observed for pigmentary changes as well. Direct intraocular extension of eyelid tumors is extremely rare, but fundoscopy may reveal signs of ocular or orbital involvement (choroidal folds, venous congestion) in suspected cases.

Diagnostic Evaluation

Ancillary Laboratory and Imaging Studies

History and physical examination of a suspected eyelid tumor occasionally dictates ancillary testing. In cases of suspected eyelid granulomas, inflammatory labs may be indicated such as antinuclear cytoplasmic antibodies (p-ANCA/c-ANCA) and angiotensin-converting enzyme (ACE) to rule out more specific causes of inflammation. If the examination reveals associated orbital or lacrimal outflow signs, computed tomography (CT) or magnetic resonance imaging (MRI) may help to determine the extent of the lesion. Schirmer testing could be considered to document underlying dry eye disease. Lacrimal probing and irrigation should be performed for peri-punctal lesions, for lesions in proximity to the nasolacrimal drainage system, and for patients with preexisting epiphora. Photodocumenation of the lesion and periorbita should also be performed, especially prior to biopsy. Marking the lesion and taking a photograph is helpful in localization if further procedures or monitoring are needed.

Dermatoscopy

Dermatoscopy is an in vivo noninvasive technique that may improve the clinical accuracy in diagnosing melanoma and other pigmented skin lesions [3]. Optical coherence tomography (OCT) may represent a new and promising technique for noninvasive investigation of skin tumors [4]. This modality may not only distinguish tumor tissue from normal tissue but may also visualize the epidermis, the dermoepidermal junction, and the dermis, as well as hair follicles, blood vessels, and sweat glands [5]. Although noninvasive techniques may improve diagnostic accuracy, the clinical diagnosis of eyelid tumors remains imperfect, and biopsy still represents the gold standard.

Biopsy

Based on clinical examination, the clinician is accurate in diagnoses in a high percent of patients anywhere from 83.7% to 96.9% [6, 7]. When the lesion is clinically misdiagnosed, it is often thought the lesion is benign but in fact histologically malignant. Malignant lesions can be clinically misdiagnosed as benign, especially when they are small and have nondescript surface features, thereby emphasizing the need for a confirmatory histology via incisional or excisional biopsy [6, 7].

The goal of biopsy is to determine the pathologic nature of the lesion, while minimizing adverse functional and cosmetic consequences. Tumor location and the presumptive clinical diagnosis largely dictate the approach and technique. Shave biopsy or excisional biopsy can be performed of lesions to determine pathology.

Biopsy-proven epidermal malignancies require margin-controlled excision and repair, with either frozen section control of Moh's micrographic surgery. Melanoma, sebaceous cell carcinoma, and Merkel cell carcinoma

require excision with wide margins. Some tumors, such as capillary hemangioma, may resolve spontaneously or require nonsurgical treatment (Chap. 10).

Treatment Planning

Information gathered from the history and eyelid examination determines the initial surgical plan for biopsy. This information also determines whether any special studies on the biopsy specimen are required. Any testing specific for the suspected diagnosis should be communicated to the pathologist in advance. For example, if sebaceous carcinoma is suspected, then the specimen usually is sent fresh for Oil Red O staining; however, it can be evaluated with immunohistochemistry on paraffin section with adipophilin and androgen receptor depending on the pathologist's preference [8]. If suspicion for lymphoproliferative disease exists, a fresh specimen for immunohistochemistry and cytology may be indicated. Such foresight may avoid inconclusive biopsy results, the need for an additional tissue biopsy, and lost time.

A detailed eyelid examination may also increase the efficiency of any anticipated surgery by determining the probable extent of tumor burden. For instance, if examination points to a larger, possibly infiltrating lesion rather than a smaller, localized process, the examination may dictate map biopsies to determine the extent of the lesion. Conversely, if examination shows a small, discreet lesion, then it may call for excisional biopsy to minimize the number of surgical interventions. Shave biopy is also widely used and allows for examination of the tissue without significant disruption. The downside of shave biopsy is evaluation of the pathology at the depth of the lesion is sometimes inadequate. The examination results can direct the patient discussion to illuminate surgical risks and realities.

Conclusion

A systematic approach to the evaluation of suspected eyelid neoplasia allows the clinician to diagnose and treat these tumors efficiently and effectively. Current clinical diagnostic techniques remain inaccurate, and the threshold for biopsy should remain quite low. In the future, we hope less invasive diagnostic and therapeutic techniques will be available, as well as for improved preventive options and better early detection to limit the morbidity of these common tumors.

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Eyelid Tumors: Classification and Differential Diagnosis

2

Jacob Pe'er and Shahar Frenkel

Introduction

In spite of being a small organ, the eyelids contain numerous histological elements that can be the origin of several types of benign or malignant tumors. In this chapter, we review the basic anatomy of the eyelid, outline a clinically relevant classification of eyelid tumors, and briefly discuss their differential diagnosis.

Anatomical Features

The eyelids are composed of four layers: skin and subcutaneous tissue, striated muscle (orbicularis oculi), tarsus, and conjunctiva [1]. The rest of the orbital entrance, which clinically may be considered as part of the eyelids, is covered, behind the skin and the orbicularis muscle, by the orbital septum that holds back the orbital fat.

Eyelid Skin

The eyelid skin, especially the lower eyelid, is among the most sunlight-exposed anatomical structures. The eye and the eyelids are one of the most observed parts of the face, and therefore, eyelid tumors are usually diagnosed at an early stage. The eyelid skin is the thinnest in the body and lacks subcutaneous fat, but otherwise contains all other skin structures. In the pretarsal part, the skin and orbicularis oculi muscle are normally firmly attached to the tarsal plate, whereas in the preseptal part, they are more loosely attached. The skin epithelium is keratinized stratified squamous epithelium, the origin of all types of benign and malignant epidermal tumors. Melanocytes are spread in the basal layer of the epithelium and may give rise to melanocytic cutaneous lesions. The dermis contains also fibrous tissue, blood and lymphatic vessels, and nerves that can give rise to many types of fibrous tissue tumors, fibrohistiocytic tumors, vascular tumors, and neural tumors.

Adnexal Glands

The eyelids are rich in glandular tissue that may be the origin of various glandular tumors. Eccrine gland tumors may arise from the sweat glands of the eyelid skin as well as from the accessory lacrimal glands of Krause and

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Wolfring. The glands of Moll can give rise to apocrine tumors. The sebaceous glands of Zeiss and the meibomian gland are the origin of sebaceous gland tumors.

Orbicularis Oculi

The entire orbital entrance is covered by the orbicularis oculi—a striated muscle that is divided into pretarsal and preseptal zones which are part of the eyelids and are involved in the eyelid movements and the orbital zone that is located over the external orbital bones.

Tarsus

The tarsi are firm plates composed of dense connective tissues that serve as the skeleton of the eyelids. The upper tarsal plates are much larger than the lower ones. The meibomian glands, large sebaceous glands, are embedded in the connective tissue of the tarsal plates. The superior tarsal muscle (Muller's muscle), a smooth muscle, is attached to the upper margin of the tarsus. A parallel muscle does not exist in the inferior tarsus, but the aponeurosis of the inferior rectus muscle attaches to the inferior edge of the inferior tarsus. The upper and lower orbital septum, a thin sheet of fibrous tissue, arises from the periosteum in the orbital rim and fuses with the levator aponeurosis superiorly and the lower margin of the lower tarsus inferiorly. All these histological structures can give rise to rare fibrous, striated, and smooth muscular and glandular tumors. The orbital fat behind the septum and the fat under the orbital part of the orbicularis oculi can be the origin of rare lipomatous tumors.

Palpebral Conjunctiva

The posterior eyelid surface is lined by the conjunctiva—a translucent mucous membrane that is composed of epithelium and subepithelial stroma—the substantia propria. The anatomical and histological features of the conjunctiva and the possible tumors that can originate from this tissue are described elsewhere (Chap. 12).

Eyelid Margin

The eyelid margin is a flat area on the edge of each eyelid. The anatomical structures that are seen in the margin from the skin backwards are the eyelashes and their lash follicles, the gray line which consists of the tips of the pretarsal orbicularis muscle (the muscle of Riolan), the meibomian gland orifices, and the mucocutaneous junction just posterior to them.

Vascular System

The venous and lymphatic drainage is important in understanding the routes of possible eyelid tumor metastases. The eyelid has extensive vascularity that comes from two main sources— the internal carotid and external carotid arteries—with anastomoses between these two systems. The venous drainage is into the angular vein medially, superficial temporal vein laterally, and the orbital veins, anterior facial vein, and the pterygoid plexus posteriorly. The lymphatic drainage of the medial portions of the eyelids is into the submandibular lymph nodes and of the lateral portions into the superficial preauricular nodes and then into the deeper cervical nodes.

Nerve Supply

The sensory nerve supply to the eyelids is from the fifth cranial nerve, and the motor nerve supply to the striated muscles is from the third and seventh cranial nerves and to the smooth muscles from sympathetic nerves.

Classification of Eyelid Tumors

Tumors of the eyelid may be classified, like tumors in other organs, according to their tissue or cell of origin and as benign or malignant. In

most groups of tumors, unique histological subtypes behave differently in spite of being of the same cell of origin.

The classification of eyelid tumors that appears in this section is based primarily on the second edition of the World Health Organization (WHO) International Histological Classification of Tumors (Table 2.1) [2]. The epithelial tumor classification has been modified and divided into groups according to the tumor cell of origin. Some tumors that are missing from the WHO list have been added from other sources [3–5].

The vast majority of the eyelid tumors, benign and malignant, are of cutaneous origin, mostly epidermal. These tumors are divided into non-melanocytic and melanocytic tumors (Table 2.2). Benign epithelial proliferations, basal cell carcinoma, cystic structures, and melanocytic nevi represent about 85% of all eyelid tumors [6, 7]. The squamous cell carcinoma and the melanoma are relatively rare [7]. Tumors arising from adnexal structures (Table 2.3), fibrous tissue, fibrohistiocytic and muscular tumors (Table 2.4), and other stromal tumors (Tables 2.5 and 2.6) are less frequent. Lymphoid tumors, hamartomas and choristomas, and inflammatory and infectious lesions that simulate neoplasms are listed in Table 2.7.

Table 2.1 Major types of eyelid tumors

Category	Subtypes
Epidermal tumors	Non-melanocytic tumors
	Melanocytic tumors
Adnexal tumors	Sebaceous gland tumors
	Sweat gland tumors
	Lacrimal gland tumors
	Hair follicle tumors
	Cystic lesions
Stromal tumors	Fibrous tissue tumors
	Fibrohistiocytic tumors
	Lipomatous tumors
	Smooth muscle tumors
	Skeletal muscle tumors
	Vascular tumors
	Perivascular tumors
	Neural tumors
	Lymphoid, plasmacytic, and leukemic tumors
	Cartilage and bone tumors
	Hamartoma and choristoma
	Palpebral conjunctival tumors
Secondary tumors	
Metastatic tumors	
Inflammatory and infectious lesions that simulate neoplasms	

Differential Diagnosis

Various characteristics of the tumor and the patient's general health are important in making the correct diagnosis. The important features that should be noted in examining the eyelid tumor are the tumor location (upper or lower eyelid, inner or outer canthus); is it on the eyelid margin; the eyelid layer involved (skin, subcutaneous tissue, or palpebral conjunctiva); is the tumor solid or cystic; tumor size; the color of the lesion (pigmented or non-pigmented); skin color (red, pink, yellow, white, or blue); the tumor consistency (hard, soft, or rubbery); its surface (smooth, irregular, papillary, ulcerated, umbilicated, cratered, or keratinized); its shape (flat or raised, pedunculated, papillary); is the tumor thin or thick; is the tumor solitary or are there several or multiple tumors; is there loss of eyelashes; the patient's race, age, and gender; is the tumor movable with the skin or is it fixed to the subcutaneous layers; the existence of systemic diseases such as genetic diseases (e.g., neurofibromatosis) or systemic malignancies; and the existence of diseases or malignancies in the surrounding structures (the eyeball, conjunctiva, orbit, lacrimal drainage system, and neighboring skin).

Certain features of the tumor are suggestive of malignancy [5]. Development of a new lesion or changes in size, shape, color, or surface appearance of an existing lesion is suspicious for malignant conversion. Poorly defined borders, palpable induration beyond visible boundaries, loss of fine cutaneous rhytids, hypervascularity, ulceration, and destruction of the normal eyelid architecture are all worrisome. Lesions that are not freely mobile due to invasion of underlying structures and those associated with regional lymphadenopathy, hypesthesia, paresthesia or pain, indicating

Table 2.2 Classification of epidermal tumors of the eyelid

Category	Subtypes	
Non-melanocytic	Benign	Squamous cell papilloma
		Seborrheic keratosis
		Inverted follicular keratosis
		Reactive hyperplasia (pseudoepitheliomatous hyperplasia)
	Premalignant	Actinic (solar) keratosis
		Intraepithelial neoplasia
		Sebaceous nevus (of Jadassohn)
		Xeroderma pigmentosum
	Malignant	Basal cell carcinoma
		Squamous cell carcinoma
		Mucoepidermoid carcinoma
		Keratoacanthoma
Melanocytic	Epithelial pigmentation	Ephelis or freckles
		Lentigo simplex
		Solar lentigo
	Benign	Junctional nevus
		Intradermal nevus
		Compound nevus
		Spitz nevus
		Balloon cell nevus
		Blue nevus
		Cellular blue nevus
		Oculodermal nevus of Ota
	Premalignant	Congenital dysplastic nevus
		Lentigo maligna (melanotic freckle of Hutchinson)
	Malignant	Melanoma arising from nevi
		Melanoma arising in lentigo maligna
		Melanoma arising de novo

Table 2.3 Classification of adnexal and cystic tumors of the eyelid

Category	Subtypes	
Sebaceous gland tumors	Benign	Sebaceous gland hyperplasia
		Sebaceous gland adenoma
	Malignant	Sebaceous gland carcinoma
Sweat gland and lacrimal gland tumors	Benign	Syringoma
		Papillary syringadenoma
		Eccrine spiradenoma
		Eccrine acrospiroma
		Pleomorphic adenoma (benign mixed tumor)
		Eccrine cylindroma
		Apocrine adenoma
		Other benign tumors
	Malignant	Sweat gland (eccrine) adenocarcinoma
		Mucinous sweat gland adenocarcinoma
		Apocrine gland adenocarcinoma
		Adenoid cystic carcinoma
		Porocarcinoma
Hair follicle tumors	Benign	Trichoepithelioma
		Trichofolliculoma/trichoadenoma
		Trichilemmoma
		Pilomatrixoma (calcifying epithelioma of Malherbe)
	Malignant	Carcinoma of hair follicles

Table 2.3 (continued)

Category	Subtypes	
Other cystic lesions	Benign	Epidermal inclusion cyst
		Sebaceous cyst
		Retention cyst
		Eccrine hidrocystoma
		Apocrine hidrocystoma
		Trichilemmal cyst
		Other benign cystic lesion

Table 2.4 Classification of fibrous, fibrous histiocytic, and muscular tumors of the eyelid

Origin	Type	Tumor
Fibrous	Benign	Fibroma
		Keloid
		Nodular fasciitis
		Proliferative fasciitis
		Fibromatosis
	Malignant	Fibrosarcoma
		Congenital fibrosarcoma
Fibrous histiocytic	Benign	Xanthelasma
		Xanthoma
		Dermatofibroma
		Xanthogranuloma
		Fibrous histiocytoma
		Juvenile xanthogranuloma
		Necrotic xanthogranuloma
		Reticulohistiocytoma
	Intermediate	Atypical fibroxanthoma
		Dermatofibrosarcoma protuberans
		Angiomatoid fibrous histiocytoma
	Malignant	Malignant fibrous histiocytoma
		Malignant giant cell fibrous histiocytoma
		Malignant fibroxanthoma
Smooth muscle	Benign	Leiomyoma
		Angiomyoma
	Malignant	Leiomyosarcoma
Skeletal muscle	Benign	Rhabdomyoma
	Malignant	Rhabdomyosarcoma

lymphatic or perineural spread are also suspicious for malignancy. Lesions associated with chronic inflammation that respond partially or temporarily to topical corticosteroids or antibiotics also may harbor malignancies. However, one should keep in mind that on the one hand malignant tumors can appear without any worrisome signs, while totally benign tumors can express some of the abovementioned features.

Table 2.5 Classification of vascular and perivascular tumors of the eyelid

Category	Subtypes	
Vascular	Benign	Nevus flammeus (port wine stain)
		Papillary endothelial hyperplasia
		Capillary hemangioma
		Cavernous hemangioma
		Venous hemangioma
		Epithelioid hemangioma (angiolymphoid hyperplasia)
		Arteriovenous malformation
		Lymphangioma
	Malignant	Angiosarcoma
		Lymphangiosarcoma
		Kaposi's sarcoma
Perivascular	Benign	Hemangiopericytoma
		Glomus tumor
	Malignant	Malignant hemangiopericytoma
		Malignant glomus tumor

Table 2.6 Classification of neural, lipomatous, cartilage, and bone tumors of the eyelid

Category	Subtypes	
Neural	Benign	Traumatic neuroma
		Neurofibroma
		Plexiform neurofibroma
		Schwannoma (neurilemoma)
		Others, e.g., neuroglial choristoma
	Malignant	Malignant peripheral nerve sheath tumor
		Merkel cell tumor
Lipomatous	Benign	Lipoma
		Others, e.g., hibernoma
	Malignant	Lilposarcoma
Cartilage and bone	Benign	Chondroma
		Osteoma
	Malignant	Chondrosarcoma
		Mesenchymal chondrosarcoma
		Osteosarcoma

Table 2.7 Classification of lymphoid tumors, hamartomas, choristomas, and inflammatory and infectious lesions that simulate neoplasms

Category	Subtypes
Lymphoid	Benign lymphoid hyperplasia
	Lymphoma
	Plasmacytoma
	Leukemic infiltration
Hamartomas and choristomas	Dermoid cyst
	Phakomatous choristoma
	Ectopic lacrimal gland
Inflammatory and infectious lesions	Chalazion
	Pyogenic granuloma
	Verruca vulgaris
	Molluscum contagiosum
	Others
Others	e.g., myxoma

Epidermal Non-melanocytic Tumors

The most common benign epithelial tumor is the squamous papilloma that is often sessile or pedunculated with papillary shape and keratinized surface (Table 2.2). Squamous papillomata may be multiple. Other epithelial tumors, including the premalignant actinic keratosis or small squamous cell carcinoma may look similar. Basal cell carcinoma comprises over 90% of all malignant eyelid tumors [7]. Its common location is the lower eyelid and medial canthus; it is usually firm and often has an ulcerated center. Other ulcerated eyelid tumors, such as keratoacanthoma or the more rare papillary syringadenoma, should be differentiated from BCC. Features of keratoacanthoma, such as rapid growth and possible spontaneous regression, can help in its diagnosis. Staging of carcinomas of the eyelid skin and adnexa can be found in the AJCC Cancer Staging Manual [8].

Epidermal Melanocytic Tumors

The most common pigmented eyelid lesions are the nevi, which are usually flat or mildly elevated and can appear anywhere in the eyelid in any size, and when appearing on the eyelid margin can be sessile (Table 2.2). Congenital nevi usually appear at birth and acquired nevi between the ages of 5 and 10 years. Nevi should be differentiated on the one hand from flat epithelial pigmentation such as ephelis or freckles and, on the other hand, from the flat premalignant lentigo maligna or from malignant melanoma that is relatively rare in the eyelids.

Adnexal and Cystic Tumors

The eyelid adnexa include many different glands that are the origin of various benign and malignant tumors (Table 2.3). These include cystic lesions such as eccrine and apocrine hidrocystoma that are totally benign and may be transparent or have a distinct color like the blue apocrine hidrocystoma. On the other hand, there are very malignant solid sebaceous gland carcinomas that may resemble chalazion but unlike chalazion cause loss of eyelashes.

Stromal Tumors

The stromal eyelid tumors usually have a smooth surface, being under the skin (Tables 2.4, 2.5, and 2.6). The tumor elevation may have normal skin color, but many of the tumors will have a distinct color. Xanthomatous lesions are usually yellow. Most hemangiomas, diffuse or localized, are red. Subcutaneous varix is soft and blue, and Kaposi's sarcoma is blue or red. Merkel cell tumor is red or violaceous. Eyelid lymphoma can be manifested as a smooth, firm subcutaneous nodule. Sometimes also subcutaneous tumors can be sessile or even ulcerated, so such phenomena, which are usually seen in epidermal tumors, should not exclude them.

Inflammatory and Infective Simulating Conditions

In the differential diagnosis of eyelid tumors, we should include lesions that simulate tumors (Table 2.7). The most common simulating lesions

are inflammatory lesions such as chalazion or pyogenic granuloma (a misnomer for granulation tissue) or infectious viral lesions such as molluscum contagiosum or verruca vulgaris that is clinically and histologically similar to squamous papilloma. Many dermatological diseases such as amyloidosis and malakoplakia or connective tissue disease and systemic metabolic diseases such as hemachromatosis may, sometimes, simulate eyelid tumors and should be differentiated from them.

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3 Benign Eyelid Squamous and Melanocytic Tumors

Lynn Schoenfield and Arun D. Singh

Introduction

The eyelid consists of six layers with epidermis externally and palpebral conjunctiva internally. Between these two (from outer to inner) are dermis, loose subcutaneous layer, orbicularis muscle, and tarsal plate. The epithelium consists of squamous cells and melanocytes primarily with smaller numbers of Langerhans cells and Merkel cells. The presence of Langerhans cells is important to recognize, as they, like melanocytes, are positive for the immunohistochemical stain S100. Benign tumors of the eyelid include a variety of nonpigmented and pigmented epidermal tumors, which arise from squamous and melanocytic cells, respectively, adnexal tumors (Chap. 4), stromal tumors (Chap. 5), and benign lymphoid proliferations. Important to note is that not all clinically pigmented lesions are melanocytic, since squamous cell proliferations can include scattered melanocytes or melanin pigment, thus giving a pigmented appearance to a lesion. The benign epidermal tumors of the eyelid are similar to those observed in the other sun-exposed areas of the skin, but they may also include conjunctival tumors as well. Some of these tumors represent manifestations of systemic disease (Chap. 11). A classification of the epidermal eyelid tumors is presented in Table 3.1. Only the description of the most common and frequently observed benign tumors, along with their corresponding premalignant lesions and tumor-like nonneoplastic lesions, is included in this chapter.

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Squamous (Non-melanocytic) Tumors

Squamous Cell Papilloma

Squamous papillomas are the most common benign tumors typically occurring in middle-aged or older adults. The clinical appearance is that of a pedunculated or sessile nodular growth with a variably convoluted surface with or without hyperkeratosis. They are often multiple, present at the lid margin, and are skin-colored (Fig. 3.1a) [1].

Microscopically a papilloma consists of benign squamous hyperplastic (acanthotic) epithelium with variable hyperkeratosis or parakeratosis overlying an expanded fingerlike fibrovascular core, which creates the exophytic nodule. They sometimes have overlapping features with seborrheic keratosis (Fig. 3.1b). If symptomatic, surgical excision may be performed.

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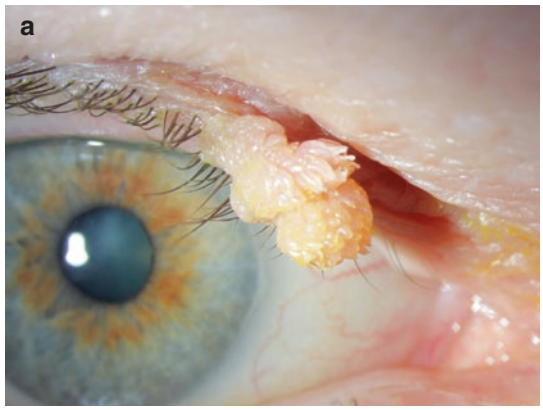
Table 3.1 Classification of epidermal tumors of the eyelid, excluding adnexal tumors

Types	Subtypes	
Non-melanocytic	Benign	Squamous cell papilloma
		Seborrheic keratosis
		Inverted follicular keratosis
		Molluscum contagiosum
		Reactive hyperplasia (pseudoepitheliomatous hyperplasia)
	Potentially premalignant	Actinic (solar) keratosis
		Intraepithelial neoplasia
		Sebaceous nevus (of Jadassohn)
	Malignant	Basal cell carcinoma
		Squamous cell carcinoma
Melanocytic	Benign epithelial pigmentation or hypermelanosis	Ephelis or freckles
		Lentigo simplex
		Solar lentigo
	Benign	Junctional nevus
		Intradermal nevus
		Compound nevus
		Spitz nevus
		Balloon cell nevus
		Blue nevus and cellular blue nevus
		Oculodermal nevus of Ota
		Seborrheic keratosis
	Potentially premalignant	Congenital dysplastic nevus
		Lentigo maligna (melanotic freckle of Hutchinson)
	Malignant	Melanoma arising from nevi
		Melanoma arising in lentigo maligna
		Melanoma arising de novo



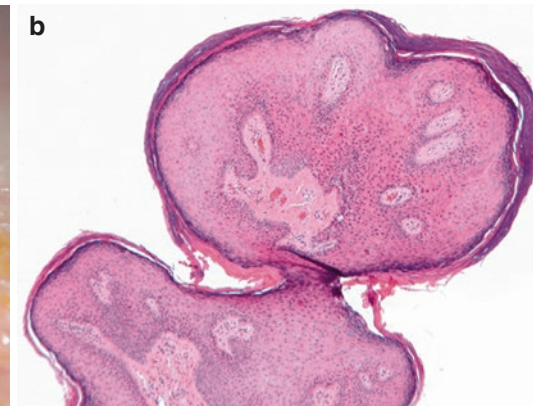


Fig. 3.1 Squamous papilloma. Clinical appearance. (**a**) Polypoid lesion consisting of benign squamous epithelium with variable acanthosis and hyperkeratosis overlying a fibrovascular core ((**b**) hematoxylin and eosin; original magnification 4×)

Seborrheic Keratosis

Seborrheic keratoses are commonly acquired skin lesions which can occur on the eyelid affecting middle-aged and elderly patients. They have also been referred to as basal cell papilloma, seborrheic wart, and senile verruca. The clinical appearance varies considerably in terms of size (few millimeters to several centimeters) and degree of pigmentation making it sometimes

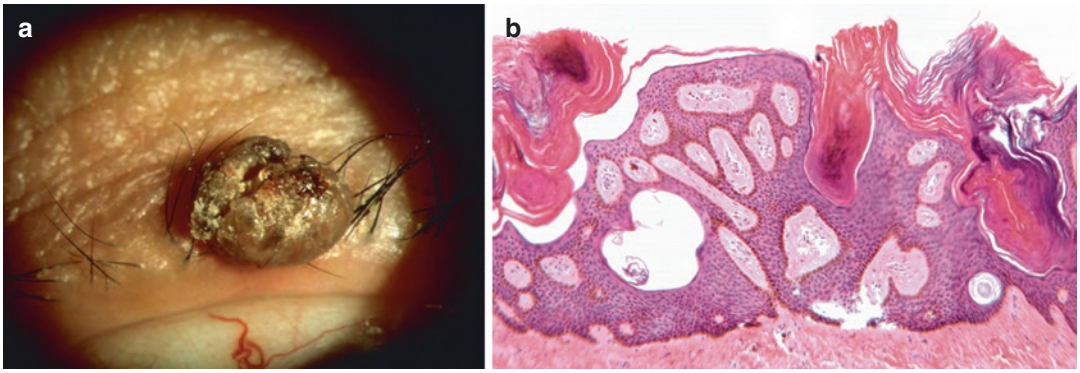


Fig. 3.2 Seborrheic keratosis. Upper eyelid involvement in a 75-year-old man. (**a**) Retiform (network-like) pattern of squamous epithelium surrounding islands of connective tissue and composed of sheets of basaloid cells with keratin-filled horn pseudocysts ((**b**) hematoxylin and eosin; original magnification 10×)

difficult to differentiate clinically from nevi, pigmented basal cell carcinomas, and melanoma [1]. They are sharply demarcated warty plaques or dome-shaped growths with a greasy and cerebriform surface, which may become friable with inflamed eczema-like features (Fig. 3.2).

Seborrheic keratoses are divided into several histological types according to the predominant histologic features: acanthotic, hyperkeratotic, adenoid (reticulated), clonal, and irritated (Fig. 3.2).The most common type is the acanthotic, in which there is a proliferation of squamous basaloid cells protruding above the skin surface, which is punctuated by horn pseudocysts. Typically, the basal plane of the lesion is in alignment with the surrounding uninvolved squamous epithelium. Hyperpigmentation can occur, which is due to transfer of melanin to the keratinocytes. When a patient experiences a sudden appearance of a seborrheic keratosis or an increase in the number or size of these lesions, this may be associated with an internal malignancy and is referred to as the Leser-Trelat sign [2, 3]. Even in lesions that are large, the growth pattern is superficial with growth predominantly above the epidermal surface. Therefore, deep excision is unnecessary; and these lesions are often removed by shave biopsy.

Inverted Follicular Keratosis

Inverted follicular keratosis is a somewhat controversial entity, as some consider it to be a variant of seborrheic keratosis or verruca vulgaris. It is commonly seen on the face, particularly the cheeks, upper lip, and less often, eyelid [4–7]. It usually occurs in older men and ranges in size from 0.3 to 1.0 cm. Usually a solitary lesion of recent onset (less than 3 months), it may be nodular, papillomatous, or cystic in appearance. Inverted follicular keratosis may recur following incomplete excision and thus be easily mistaken for squamous cell carcinoma [7].

Histopathologically, there are four main growth patterns: papillomatous, keratoacanthoma-like, solid nodular form, or cystic type. Usually it consists of an endophytic proliferation of squamous epithelium with squamous eddies, hyperkeratosis, parakeratosis, acantholysis, generally little if any melanin pigment, and dermal chronic inflammation. There may be increased mitoses and apoptosis (Fig. 3.3) [6, 7]. Complete excision should be performed to prevent recurrence.

Molluscum Contagiosum

Molluscum contagiosum is an on neoplastic skin infection caused by a virus from the pox virus group. This entity occurs frequently in children but may also occur in adults anywhere on the body except the palms and soles. It appears as papules that are white- or flesh-colored measuring 2–5 mm, often with a central dimple or plug containing cheesy or waxy material (Fig. 3.4).

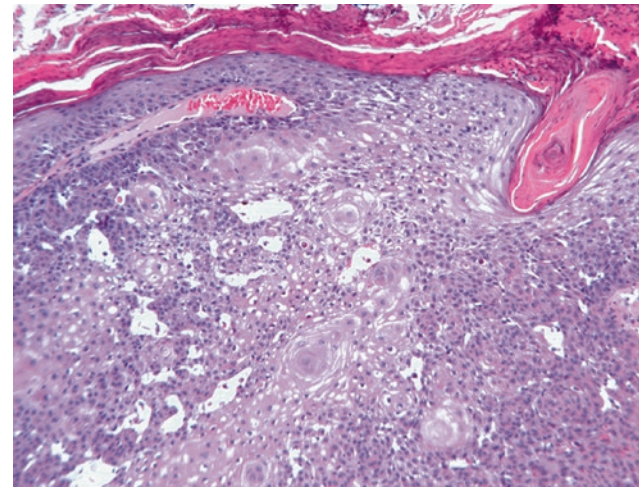


Fig. 3.3 Inverted follicular keratosis. Note endophytic growth pattern with overlying hyperkeratosis and parakeratosis. Flattened concentric epidermal cells within acanthotic areas are called squamous eddies (hematoxylin and eosin; original magnification 10×)

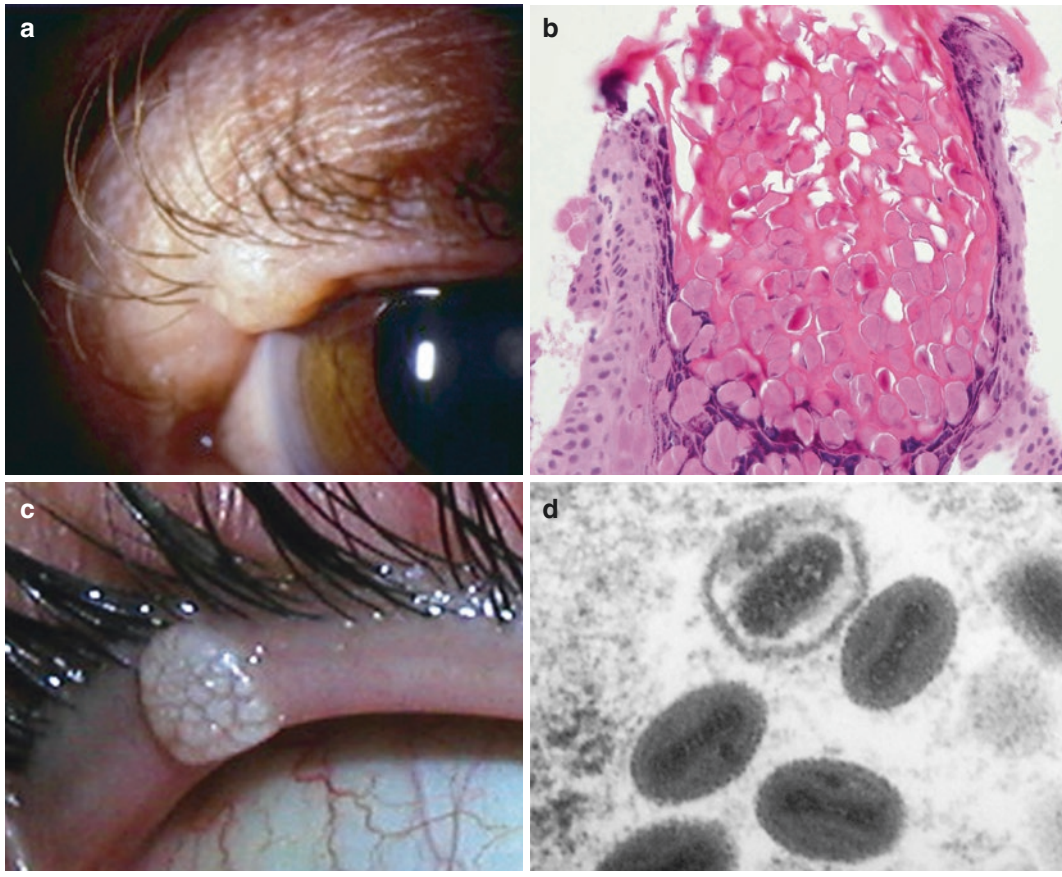


Fig. 3.4 Molluscum contagiosum. Clinical appearance. (**a**) Epidermal crater filled with keratinocytes containing molluscum bodies (intracytoplasmic inclusions). ((**b**) hematoxylin and eosin; original 40× magnification). (**c**) The clinical presentation of a conglomerated lesion which is well-demarcated, white, sessile lesion located on the grey line. (**d**) A molluscum contagiosum virus under electron microscopy. (**c**, **d**): (Reprinted from Rosner and Zloto [8]. With permission from John Wiley & Sons)

Molluscum contagiosum is characterized by downward growth of hyperplastic epidermis, sometimes forming multiple lobules. The keratinocytes contain large eosinophilic intracytoplasmic inclusion bodies ("molluscum bodies"), which enlarge as they reach the surface and become more basophilic (Fig. 3.4). The central crater consists of disintegrating cells discharging the molluscum bodies and keratin [8]. These lesions usually resolve over months to years in patients with intact immune systems. However, removal of individual lesions can be done surgically or by scraping, decoring, freezing, or electrosurgery. Medications used for warts may also be used, and cantharidin ("beetle juice") is the most common solution used. Tretinoin cream is an alternative.

Keratoacanthoma

Keratoacanthoma has a complicated history and has been classified both as benign and malignant (self-healing squamous cell carcinoma or squamous cell carcinoma, keratoacanthoma-type). The latter is favored in many countries. However, in some literature, it has been noted to sometimes spontaneously regress and thus considered to be a benign lesion [9–12]. Typically a keratoacanthoma is a solitary-, pink-, or flesh-colored, dome-shaped nodule with a central keratin crater, arising on sun-exposed skin of an elderly individual. There may be rapid growth to 1 or 2 cm over the course of 2–10 weeks. This is followed by a stationary period of similar duration and then involution over the course of 8–50 weeks or more.

The histologic features needed for a confident diagnosis require assessment of the entire lesion, so as not to miss an infiltrating squamous cell carcinoma at the base. The tumor is cup- or crater-shaped and consists of centrally proliferating well-differentiated squamous cells with strongly eosinophilic cytoplasm that enlarge in the center of the tumor nests. Often there is a central keratin plug, and there may be neutrophilic abscesses in the epithelium. At the periphery, the epithelium forms symmetrical "lips" or "buttresses" which overhang the crater. The underlying dermis is usually inflamed but without desmoplasia, unless the lesion is involuting. Deeper sections are recommended in order to rule out the possibility of typical infiltrating squamous cell carcinoma, which may be focal in an otherwise classic picture of keratoacanthoma (thus the term "keratoacanthoma-like squamous cell carcinoma") [12]. Complete excision should be performed.

Reactive Hyperplasia (Pseudoepitheliomatous Hyperplasia)

Squamous epithelial hyperplasia occurs as a reaction to trauma, surgical wound, cryotherapy, burn, radiation, ulcers, or fungal infection [13]. It can also occur in association with tumors such as granular cell tumor and melanocytic lesions. It is not a tumor but rather a reactive process that may clinically be seen as a tumor.

Histopathology can be challenging as well. An elevated nodular or ulcerative lesion resembling basal or squamous cell carcinoma. There may be an ulcer.

There is squamous hyperplasia with elongated, irregular, and sometimes anastomosing rete pegs (rete ridges) which may resemble invasive tongues or nest of squamous carcinoma. Cellular nests may be contain neutrophilic microabscesses, especially when associated with infection (Fig. 3.5) [14]. The epithelium shows normal maturation without true dysplasia; however, there may be cytologic atypia and even mitoses, further complicating the distinction from carcinoma. Complete excision is recommended when clinically suspicious.

Cutaneous Horn or Nonspecific Keratosis

These are nondiagnostic descriptive terms for any hyperkeratotic lesion (benign or malignant) and thus do not imply by themselves predilection for malignant behavior. A protruding keratotic lesion is the presentation (Fig. 3.6). This lesion is

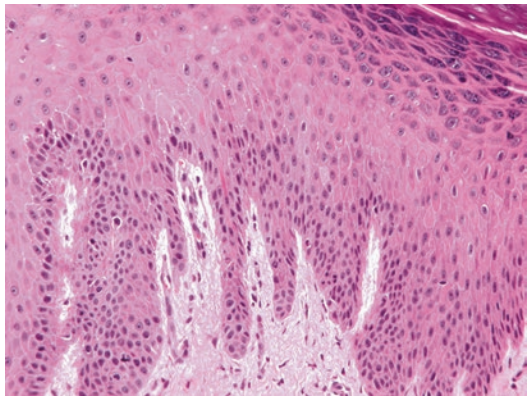


Fig. 3.5 Reactive hyperplasia (pseudoepitheliomatous hyperplasia). Epidermal (squamous) hyperplasia with elongated and sometimes anastomosing rete ridges, normal maturation of epithelium, and variable hyperkeratosis. Note the absence of atypia in this case (hematoxylin and eosin; original magnification 20×)

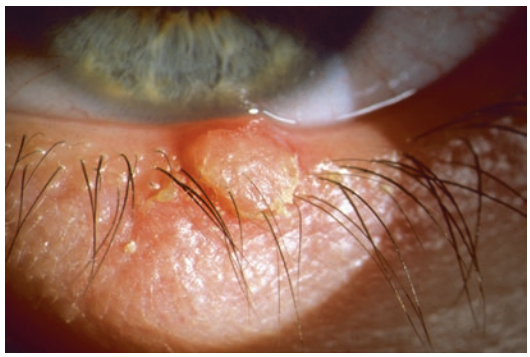


Fig. 3.6 Cutaneous horn is a clinically descriptive, nondiagnostic term for a nonspecific keratosis

associated with a variety of benign or malignant lesions. In a study of 48 cases [6] involving the eyelids, 77.1% were associated with found to be benign on histopathology, 14.6% were premalignant, and 8.3% were malignant skin tumors. The most common associated lesions were seborrheic keratosis, actinic keratosis, basal cell carcinoma, and squamous cell carcinoma [15, 16].

There are no specific histopathologic features other than hyperkeratosis, with or without parakeratosis. The keratosis (or horn) by itself is not diagnostic, but rather the features of the squamous epithelium giving rise to the keratosis are the defining factors as to the biologic behavior of the lesion [15]. Treatment should be determined by the histopathology if possible. If the lesion is clinically suspicious for malignancy, excision is recommended.

Sebaceous Nevus (of Jadassohn)

Sebaceous nevus syndrome (of Jadassohn), an uncommon congenital lesion, is part of the epidermal nevus syndrome and characterized by cutaneous sebaceous nevi and extracutaneous manifestations. It is a benign hamartoma composed of large sebaceous glands, heterotopic apocrine glands, defective hair follicles, acanthosis, and papillomatosis. These lesions evolve with time. They are most commonly found on the head and neck region and appear as irregular linear lesions with alopecia (Fig. 3.7). In spite of their being benign, there is an increased risk in adulthood for the development of secondary benign (such as syringocystadenoma papilliferum) or malignant skin tumors (most commonly basal cell carcinoma) within the area of these nevi [17–19].

Actinic (Solar) Keratosis

Actinic or solar keratosis is most frequently a result of chronic and cumulative exposure of the epidermal cells of the skin to ultraviolet radiation (UV-B) in the form of sunlight, causing mutations to the p53 gene [20]. Fair-skinned older patients and those with a history of excessive sun exposure are typically affected. However, there is also an increased incidence in renal transplant patients, and thus immunosuppression is a risk factor [21]. There are a variety of clinical presentations, usually characterized by multiple, erythematous, scaly lesions with either discrete or diffuse borders [21]. They feel like sandpaper and may be plaque-like on palpation. Actinic keratosis has historically been considered a precursor to squamous cell carcinoma, and most now consider it to represent squamous cell carcinoma in situ or keratinocyte intraepithelial neo-