HISTOLOGICAL PATTERN OF ACQUIRED CONJUNCTIVAL GROWTHS AND THEIR RELATIONSHIP TO HIV INFECTION AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA

A Cross Sectional Descriptive Study at Muhimbili Eye Department

By

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A dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medicine (Ophthalmology) of the university of Dar es salaam.

University of Dar es salaam

October 2003.

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Dar es salaam a dissertation entitled:

Histological pattern of acquired conjunctival growths and their relationship to HIV infection at Muhimbili National Hospital, in partial fulfillment of the requirements for the degree of Master of Medicine (Ophthalmology).

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DECLARATION

AND

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I, Nkundwe Mwakyusa, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATION

To my parents, Jennifer and Gallen.

ABSTRACT

Over the past few years a considerable body of literature has reported an increase in the incidence of acquired conjunctival growths. A significant relationship to the HIV/AIDS pandemic has been shown. There is no data representative of Tanzania. This study was conducted at Muhimbili National Hospital eye departmnet to describe the histological pattern of acquired conjunctival growths and to correlate it to the HIV serological status.

The study design was cross sectional descriptive involving 120 patients obtained over a period of 8 months (May 2002-December 2002). Collected data were filled in a data sheet for each patient. Recorded data included demographic information, clinical description of the growth, histological type of growth and HIV serological status of the patient. Data were analyzed using the EPINFO6 package designed for population surveys in cross sectional studies.

The mean age of the study subjects was 35.6 years with a range of 8-80 years. 79.2% of patients were in the age group 16-45 years. Females accounted for 65% of the study population. Histologically benign growths accounted for 46.6%, premaligant 9.2% and malignant growths accounted for 44.2%. The commonest histological diagnosis was squamous cell carcinoma (32.5%), followed by pterygium (24.2%). Pingueculae and Kaposis sarcoma each accounted for 10.0% of all growths. 42.5% of patients were HIV seropositive. Conjunctival squamous cell carcinoma and Kaposis sarcoma were found to be significantly associated with HIV seropositivity (P values <0.01).

In conclusion the present findings suggest that conjunctival squamous cell carcinoma and Kaposis sarcoma are significantly associated with HIV infection. Similar findings have been obtained in other African countries.

There is need to evaluate the association between the degree of immunodeficiency caused by HIV infection and the development of conjunctival tumours for academic purposes.

Early surgical excision of suspicious conjunctival growths for histological studying is recommended.

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LIST OF ABREVIATIONS

HPV=Human Papilloma Virus

HIV=Human Immunodeficiency Virus

SCC=Squamous Cell Carcinoma

IJCN=Inflamed Juvenile Conjunctival Naevi

UV=Ultraviolet

CIN=Conjunctival Intraepithelial Neoplasia

NHL=Non Hodgkin's lymphoma

HHV=Human Herpes Virus

PCR=Polymerase Chain Reaction

NACP=National AIDS Control Programme

AIDS=Acquired Immunodeficiency Syndrome

STI=Sexually Transmitted Infections

KS=Kaposis Sarcoma

DEFINITION OF TERMS

1. **Hyperplasia :** Non neoplastic disturbance of cell growth characterized by an increase in number of cells in an organ or tissue often leading to an increased volume of that tissue.
2. **Metaplasia**: Adaptive substitution of one adult, fully differentiated, epithelial or connective tissue cell for another.
3. **Dysplasia:** Abnormal differentiation, maturation and proliferation of surface epithelial cells.
4. **Acanthosis:** Thickening of squamous layer of epithelium.
5. **Leukoplakia:** White plaque like lesion on the mucous membrane due to hyperkeratosis of the epithelium.
6. **Hyperkeratosis:** Formation and thickening of the keratin layer on the surface of the epithelium.
7. **Dyskeratosis:** Premature keratinization of individual epithelial cells before they reach the surface.
8. **Parakeratosis:** Imperfect keratinization with retention of nuclei in the surface epithelial cells.
9. **Anaplasia:** Loss of differentiation of cells and their orientation to one another and to their axial frame work and blood vessels, a characteristic of tumour tissue.

INTRODUCTION

Conjunctival growths constitute one of the ophthalmic problems necessitating hospital attendance. These growths can be benign or malignant tumours, degenerative or inflammatory hypertrophies.

The conjunctiva being the outermost covering of the eyeball, is exposed to various external factors such as mechanical, chemical, thermal, radiational, electrical or infectious. Infectious agents may be airborne or water borne or may be carried by dust, insects, fingers, towels and other fomites. These factors may play a role in the pathogenesis of a variety of conjunctival diseases.[1]

Conjunctival growths may arise from various elements of the conjunctival tissue, and may present as congenital or acquired lesions. Moreover histologically they can be benign or malignant. Malignant lesions may arise primarily from the conjunctiva or secondarily as metastases from adjacent or distant structures.

Patients often complain of a new growth. There may also be ocular discomfort, pain, redness or hyper pigmentation. Occasionally, a conjunctival growth may cause visual impairment by involving the central cornea (the visual axis) or by inducing astigmatism. Mechanical ptosis of the upper lid may be caused by growths on the upper palpebral conjunctiva while ectropion may be caused by similar growths in the lower palpebral conjunctiva. Frequently there is a history of attempted use of different types of topical medication to allay the symptoms.

Clinically it is not possible to differentiate a benign from a malignant conjunctival growth. Fortunately they are readily observable and accessible, a factor which enables surgical excision for histological studies.

Furthermore the ability of malignant lesions to appear like benign ones may favor a waiting attitude that can delay a resolutive treatment, sometimes with serious outcomes. [2]

The known predisposing and aetiological factors to development of conjunctival growths are exposure to ultraviolet light, chronic conjunctival irritation, Human Papilloma Virus (HPV) infection, cigarette smoking and exposure to petroleum products. Several authors have reported an association between conjunctival growths and Human Immunodeficiency Virus (HIV) infection. [3, 4, 5, 6] A number of studies in sub-Saharan Africa have shown an increase in the incidence of conjunctival tumours during this period of emergence of the HIV epidemic. [3, 4, 5, 6]

Conjunctival tumours have been reported as one of the ocular manifestations of HIV infection. [7, 8]

The study was carried out to describe the histological pattern of acquired conjunctival growths and to relate it to the HIV serological status.

ANATOMY OF THE CONJUNCTIVA

The conjunctiva is a thin transparent membrane that lines the inner surface of the eyelids and is reflected at the superior and inferior fornices onto the anterior surface of the eyeball. It extends from the mucocutaneous junction of the eyelid to the corneo-scleral junction(limbus). It thus forms a potential sac, the conjunctival sac which is open infront at the palpebral fissure and only closed when the eyes are shut.[9]

Although all parts of the conjunctiva are continous with each other, it is devided for descriptive purposes into three portions:

1.The palpebral conjunctiva,which lines the posterior surface of the lids and is further subdivided into 3 parts :

(a)Marginal part:A transition zone(mucocutaneous junction)between skin and conjunctiva proper.This part extends on to the back of the lid for about 2mm to a shallow groove known as the subtarsal fold at which perforating vessels pass through the tarsus to reach the conjunctiva

The puncta open into the medial part of this portion of the conjunctiva and through them the conjunctival sac becomes directly continous with the inferior meatus of the nose via the lacrimal passages.Diseases of nose may therefore spread to the conjunctiva and vice versa. [9]

(b)Tarsal part:

This part is thin,very vascular and firmly adhered to the tarsal plate.Unlike the upper tarsal conjunctiva,the lower is only firmly adhered to the tarsal plate for half the width of the tarsus. [9]

(c) Orbital part:

This lies between the upper border of the tarsal plate and the fornix.It is loosely attached to the underlying muscle of Muller.It's surface is thrown into horizontal folds which are deepest when the eyes are open and almost disappear when the eyes are shut. [9]

2.The fornicial conjunctiva.

This is a continous circular cul de sac which is broken (on the medial side)by the curuncle and the plica semilunaris.The caruncle which is more medial is a modified piece of skin and the plica semilunaris a vertical cresent of conjunctiva.The fornicial conjunctiva is devided into the following parts:

The superior fornix reaches to the level of the orbital margin some 8 to 10mm from the limbus.

The inferior fornix extends to within a few millimeters of the inferior orbital margin, 8mm from the limbus.

The lateral fornix is placed at a depth of about 5mm from the surface that is 14mm from the limbus and extends to just behind the equator of the globe.

The medial fornix is occupied by the caruncle and the plica semilunaris.

The fornicial conjunctiva is in contact with and adherent to loose fibrous tissue which is derived from facial expansions of the sheaths of the levator and recti muscles which is easly distensible.In this fibrous tissue are found the glands of Krause and the unstripped muscle of Muller. [9]

3.The bulbar conjunctiva.

This portion lines the anterior surface of the sclera.It lies loosely on the underlying tissues from which it can easily be moved.At first it is in contact with the Tenon's

capsule which covers the tendons of the recti muscles.In front of the insertions of the recti tendons,the bulbar conjunctiva lies on the anterior portion of the Tenon's capsule up to a point about 3mm from the cornea. [9]

The conjunctiva is separated from the Tenon's capsule by loose areolar tissue which contains the subconjunctival vessels and between it and the sclera is the loose episcleral tissue.In the loose episcleral tissue we find the anterior ciliary arteries which form the pericorneal plexus and the tendons of insertion of the recti muscles. [9]

At about 3mm from the cornea,the conjunctiva and the Tenon's capsule become much more closely united fusing at the limbus.

Conjunctival histology:

Like other mucous membranes the conjunctiva consists of two layers,the epithelium and the stroma or substantia propria.

(i)Conjunctival epithelium:

It is made up of 2 to 7 cell layers of stratified nonkeratinized epithelium.The cell type and number of cell layers vary from one region to another.At the mucocutaneous junction the most superficial cell layers are made up of squamous cells followed by several layers of polyhedral cells and the deepest layer consisting of cylindrical cells. [9]

As you move away from the mucocutaneous junction the total number of layers is reduced and the squamous cells are gradually replaced by the collumnar and cuboidal ones.The goblet cells also begin to appear and are particularly numerous just beyond the subtarsal fold.

The epithelium of the tarsal conjunctiva of the upper lid consist of two layers.The deeper cuboidal cell layer and the superficial layer consisting of tall cylindrical

cells.As the fornix is approached a third layer of polyhedral cells is inserted between the other two layers, and thus we find 3 layers instead of two.

The epithelium of the tarsal conjunctiva of the lower lid consists of 3 or 4 layers sometimes 5 layers may be found.

From the fornix to the limbus the epithelium becomes less and less glandular with disappearance of the Goblet cells.The superficial cells become flatter while the deeper cells grow taller.

At the limbus the basal cells form a single layer of small cylindrical or cuboidal cells with a large darkly staining nucleus and little protoplasm which produces the dark line or seam under the low power of the microscope characteristic of the limbal conjunctiva.These basal cells often contain pigment granules.Melanophores are also present in the conjunctiva of the coloured races at the limbus,at the fornix,in the plica and caruncle and at the site of perforation of the anterior ciliary vessels.In whites these cells are present but not usually pigmented. [9]

On the posterior edge of the eyelid margin,the conjunctival epithelium becomes continous with the stratified squamous keratinized epithelium of the eyelid skin and at the limbus on the other hand it becomes continous with the stratified squamous nonkeratinized epithelium of the cornea.

(ii)The substantia propria(stroma)

It is made up of two layers;a superficial adenoid layer and a deeper fibrous layer

(a)The adenoid layer:

This layer is not present at birth but is formed in the region of the fornix at 3 to 4 months of age.It consists of a fine connective tissue reticulum in which lie large

collections of lymphocytes.The layer ceases at the subtarsal fold so that lymphocytes are not found in the marginal conjunctiva.

(b)The fibrous layer

This layer is thicker than the adenoid layer but is almost nonexistent over the tarsus with which it is continous.In it are found the vessels and nerves to the conjunctiva,the unstripped muscle of Muller and the Krause's glands which are encapsulated by it.

Finger like extrusions of the substantia propria are found at the lid margins forming conjunctival papillae.

In the palpebral region the substatia propria is thin and compact enabling a firm network of septal connections to form between the epithelium and the tarsus. In the fornix it is thick and loose, but at the limbus it again thins and becomes more compact as it merges with the Tenon's capsule and episclera. [9]

Conjunctival glands:

Conjunctival glands can be grouped as follows:

(1)Mucin secreting glands:

These are of three types namely the Goblet cells,the Henle's glands and the glands of Manz.They secrete mucin which forms the inner most layer of the tear film.

(i)Goblet cells

These are true unicellular mucous glands which occur in all portions of the conjunctiva but most numerous inferonasally.They are the main mucin secretors of the conjunctiva.They are oval or round looking like fat cells. They are formed from the deepest layer of the conjunctiva and then pass towards the surface tending to remain attached to the basement membrane by a pointed process.Once they have

discharged their contents they get destroyed.Although goblet cells occur nomally in the conjunctiva they are greatly increased in inflammatory conditions.

(ii)Henle's glands

These occur in the palpebral conjunctiva between the tarsal plates and the fornices.They are not true glands but folds of mucous membrane cut transversely.

(iii)Glands of Manz

These are saccular or utricular glands found at the limbus encircling it.

(2)Accessory lacrimal glands:

These are the basic secretors of tears.They secrete the middle or acqueous layer of the precorneal tear film.

These glands are of two groups:

The glands of Krause:These are about fifty in number placed deeply in the subconjunctival connective tissue of the upper fornix.Their ducts unite into a long duct which opens into the fornix.

The glands of Wolfring are larger than the glands of Krause and situated in the upper border of the tarsal plate.There are about 5 in the upper border of the upper tarsus and 2 in the inferior edge of the lower tarsus. [9]

Blood supply of the conjunctiva:

Arterial supply:

This comes from three sources;the peripheral arterial arcades,the marginal arcades and the anterior ciliary arteries.The two arcades are formed by anastomosis of the superior and inferior medial palpebral arteries which are branches of the ophthalmic artery and the lateral palpebral arteries which are branches of lacrimal artery.The arcades are found in the submuscular areolar tissue of the eyelid.

(i)The peripheral arterial arcade:

Supplies almost the whole of the tarsal conjunctiva,the fornicial conjunctiva and the bulbar conjunctiva up to 4mm from the cornea.In the upper lid the arcade is situated at the upper border of the tarsus between the two portions of the levator muscle. Peripheral perforating branches pass above the tarsal plate and pierce the muscle of Muller to reach the conjunctiva under which they send branches upwards and downwards.

The descending branches supply the tarsal conjunctiva and anastomose with the branches of the marginal arcade which have pierced the tarsus at the subtarsal fold. [9]

The ascending branches pass upward to the fornix then bend round it and descend under the bulbar conjunctiva as the posterior conjunctival arteries.

They pass towards the cornea and at 4mm from it they anastomose with the anterior conjunctival arteries to form the anterior ciliary arteries.The posterior conjunctival vessels are mobile,moving with the bulbar conjunctiva.

In the lower lid the peripheral arcade is often absent in which case the conjunctiva of lower lid,lower fornix and inferior portion of bulbar conjunctiva get their blood supply from the marginal arcade or the muscular arteries to the inferior rectus muscle.

(ii)The marginal arcade:

This sends it's perforating branches through the tarsus to reach the deep surface of the conjunctiva at the subtarsal fold.These branches divide into marginal arterioles which run perpendicularly to the lid margin and the tarsal arterioles which run perpendicularly to meet the corresponding branches from the peripheral arcade.The tarsal conjunctiva is well supplied with blood and hence appears red.The colour

deminishes towards the fornix and the bulbar conjunctiva is colourless except when it's vessels are dilated.

(iii)The anterior ciliary arteries:

These come from muscular arteries to the recti muscles.Each muscular artery gives two anterior ciliary arteries except the one to the lateral rectus muscle which gives only one.These arteries pass forwards in a deeper plane than posterior conjunctival arteries and at about 4mm from the limbus they bend towards the interior of the eye,pierce the sclera to join the major arterial circle of the iris.At the bend,the anterior ciliaries give of anterior conjunctival arteries which pass forwards deep to the posterior conjunctival arteries. [9]

They anstomose with each other giving place to the pericorneal plexus more anteriorly. Posteriorly they send twigs which anastomose with the posterior conjunctival arteries.

Venous drainage:

Conjunctival veins accompany corresponding arteries but are much more numerous than the arteries.They drain into the palpebral veins.

Lymphatic drainage:

Lymphatics are arranged in two plexi, a superficial one,composed of small vessels placed just beneath the vascular capillaries and a deep one consisting of larger vessels situated in the fibrous layer of the conjunctiva and receiving lymph from the superficial plexus.The deep plexus vessels then join the lymphatics of the lids.Those from the lateral aspect draining to the parotid nodes and from the medial to the submandibular nodes. [9]

Nerve supply:

Nerve supply to the conjunctiva is sensory and is derived from the same source as that of the lids, that is from the ophthalmic and maxillary divisions of trigeminal nerve.The only difference from the skin sensory innervation is that the lacrimal and infratrochlear nerves supply a much larger area of the conjunctiva than that of the skin.The circumcorneal area of conjunctiva is supplied by the short ciliary nerves.

The superior bulbar,fornicial and palpebral conjunctiva from the lateral aspect medially is supplied by the ophthalmic division of trigeminal nerve via it's lacrimal,supraorbital,supratrochlear and infratrochlear branches while inferiorly from the lateral aspect medially sensory innervation is by the infraorbital branch of maxillary division of trigeminal nerve and the infratrochlear nerve. [9]

Functions of the conjunctiva:

The conjunctiva attaches the eyeball to the eyelids and allows smooth but not excessive eye movements. Intact conjunctival epithelium and its secretions forms a barrier to the entrance of exogenous infections and foreign particles. The palpebral conjunctiva helps in distributing tears and therefore lubricating the cornea through blinking. Nutrition to the sclera is provided via the conjunctiva and the subconjunctival tissues.The transportation of tears to the nasolacrimal outflow passages is aided by the conjunctiva. The conjunctiva also assists in lymphatic drainage from the eyeball to the lids. Mucin secreting cells (Goblet cells) in the conjunctiva produce the mucin layer which is the inner most layer of the tear film.This layer of the tear film coats the microvilli on the corneal surface epithelium and thus forming an even surface which is essential as far as refraction at the corneal

surface is concerned.The corneal epithelium is rendered hydrophillic from being hydrophobic by the mucin layer which is essential for maintaining the tear film on the ocular surface for the even and spontaneous distribution of the tear film. [10]

To stabilize the tear film,the mucin layer interacts with the lipid layer which is the outermost layer of the tear film in lowering the surface tension of the tear film.[10, 11]

The mucin layer is also protective to the ocular surface by it's mechanical effect of trapping foreign particles,bacteria and also exfoliated surface cells. [10, 12]

The accessory lacrimal glands of Krause and Wolfring are the basic secretors of the tears.They secrete the middle or acqueous layer of the tear film.This part of the tear film provides nutrition to the cornea(glucose) and oxygen dissolved in it from the atmosphere.Glucose and oxygen are required for corneal epithelial metabolism.

The acqueous layer also acts as a media for passage of carbondioxide and other waste products of metabolism from the cornea.Foreign particles trapped by the mucin layer are washed out by the acqueous layer. [10]

The acqueous tear film provides an access route of white blood cells from the limbal and conjunctival vessels to the central cornea. This is essential for healing of central corneal ulcers. [10]

REVIEW OF LITERATURE

EPIDEMIOLOGY OF ACQUIRED CONJUNCTIVAL GROWTHS.

Acquired conjunctival growths can be classified according to their evolution into three groups of lesions, benign lesions, lesions with possible malignant transformation and malignant lesions. The lesions in the three groups can further be subdivided according to their histological tissue of origin as epithelial or stromal. [13]

Several studies have been done in different parts of the world on the epidemiology of tumour and tumour like lesions of the conjunctiva. In Japan 126 cases of these lesions were studied. [14] 92.1%(116) were histologically benign and the rest 7.9%(10) were malignant. Of the benign lesions, pigmented nevi accounted for 27.6%. Carcinoma in situ was the most frequent malignant lesion accounting for 30% of the lesions. [14]

In another study on conjunctival lesions in adults, a clinical and histological review of 2,455 conjunctival lesions in adults (15 years or older) obtained during a 61 year period were studied. The common lesions found in order of decreasing frequency were pterygia, naevus, dysplasia, non-specific non-granulomatous inflammation and epithelial inclusion cyst. The most common malignancy was squamous cell carcinoma. [15]

ACQUIRED CONJUNCTIVAL GROWTHS AND HIV INFECTION.

A change in the epidemiological picture of acquired conjunctival growths has been reported by a number of authors who have done studies in different parts of the world including Africa, particularly Sub-Saharan Africa. [16, 17, 3, 4, 6, 18, 19, 20] Their studies have shown an increase in the incidence of malignant conjunctival tumours namely squamous cell carcinoma, Kaposis sarcoma, B-cell non Hodgkin's lymphoma and malignant melanoma over the past few years. The time period of these studies coincides with the emergence of the HIV pandemic that suggests an aetiopathogenetic role of this virus in the development of these tumours. [16, 17, 3, 4, 6, 18, 19, 20]

The number of people living with HIV/AIDS worldwide by the end of 2002 is estimated to be 42 million. [21] Seventy percent of these people (29.4 million) are reported to be in sub-Saharan Africa. Tanzania being one of the sub-Saharan countries has not been spared. HIV infection in Tanzania is unevenly distributed depending on a geographic area, gender, age, groups and socio-economic classes. [22] The percentages of population affected by HIV ranges from less than 3% across most of the country to more than 44.4% in certain sub-populations. [22] The epidemic has struck more economically active group of adults, those aged 15-45. [22]

AETIOPATHOGENESIS, CLINICAL PRESENTATION & HISTOLOGICAL FEATURES OF ACQUIRED CONJUNCTIVAL GROWTHS.

BENIGN LESIONS:

BENIGN EPITHELIAL LESIONS.

Epithelial inclusion cysts:

Solid or cystic inclusions may be implanted in the conjunctival stroma after trauma or surgical incisions. The implanted cells fail to proliferate, however on occasion the cystic inclusions progressively enlarge and form relatively large translucent cysts. Clinically they look like well-circumscribed lesions with liquid contents.

Histologically they contain desquamated cellular debris and scattered chronic inflammatory cells within a mucinous matrix. One or two layers of flattened, non-keratinizing epithelium with retained goblet cells line them. They may become secondarily infected because of their exposed location and thin walls. [23, 13]

Keratotic plaques:

These appear as white (leukoplakic), nodular, rounded masses without evidence of ulceration. They are often a result of chronic inflammation. [24] Histologically they show acanthosis which is thickening of squamous layer of epithelium, hyperkeratosis-formation of keratin layer on the surface of the epithelium or parakeratosis that is imperfect keratinization with retention of nuclei in the surface cells.

Cellular atypia is absent. [2, 25, 24]

Rarely heavily keratinized lesions resembling keratoacanthomas of the skin may occur in the bulbar conjunctiva. [24, 2, 23]

Pseudocarcinomatous hyperplasia (Pseudoepitheliomatous hyperplasia):

These present as leukoplakic changes in the conjunctival epithelium overlying pingueculae and pterygium and may lead to the clinical suspicion that squamous cell carcinoma has developed from one of these pre existing lesions. Histology shows only acanthosis, parakeratosis and/or hyperkeratosis.

Adenomas:

These are extremely rare but have been described to be growing from the Krause's glands near the upper fornix. [2] Similar growths have been found on the bulbar conjunctiva or near the limbus. Histologically they appear as normal lacrimal gland with acini and tubules sometimes showing cystic changes. [2]

Squamous papilloma:

Conjunctival papillomas are typically found in young patients. [26] They appear as bright red growths due to rich vascularization with a broad (sessile) or narrow (pedunculated) base to the sub epithelial connective tissue. They are formed by fibro vascular stromal cords covered by thickened squamous layer of the epithelium protruding from the conjunctival plane. Bulbar conjunctival lesions are usually sessile while those in other sites are pedunculated. They may have a viral aetiology (Human papilloma virus type 6&11) especially when multiple and bilateral. [13, 24]

Histology shows acanthotic squamous epithelium non-keratinized with muciparous cells. Viral aetiology is supported by presence of cells with irregular hyperchromatic nuclei and fair cytoplasm called koilocytic cells.

A variant of squamous papilloma known as inverted papilloma (mucoepidermoid benign cancer of the conjunctiva) has been described. This type of slow growing papilloma usually develops in the nose or paranasal sinus or in both. It may also

originate in the lacrimal sac or the conjunctiva. [23] It has an endophytic pattern of growth and does not infiltrate. Histologically it shows penetration of epithelial cells in the underlying connective tissue. [13]

BENIGN CONNECTIVE TISSUE LESIONS:

Fibromas:

These lesions occur rarely but constitute the commonest polypoid tumour of the conjunctiva, commonly located in the fornices, palpebral conjunctiva and at the canthi associated with the plica and caruncle. [2] They are soft, vascular, rapidly growing and bleeding readily, giving rise to "bloody tears".

Histologically they consist of masses of fibrous tissue with oval and spindle shaped young connective tissue cells infiltrated lymphocytes and leucocytes. [2]

Myxomas:

These are uncommon in the ocular area but when they occur they are located essentially in the lids and rarely in the conjunctiva. [29]

Clinically they appear as gelatinous masses with a similar appearance to malignant tumours namely botryoid rhabdomyosarcoma or fibrosarcoma.

Histology shows connective tissue cells and a mesenchyme resembling stroma. Sometimes they appear as myxofibromas. In this variation the fibrous tissue becomes oedematous as the tumour enlarges probably because of pressure of the lids on the pedicle. [2, 29]

Lipomas:

These appear as yellowish soft and elastic tumour freely movable on the conjunctiva and the sclera. Two types have been described, Lipomas in obese males over 55

years of age occurring frequently symmetrically in the upper fornix in the region of the lacrimal gland where sub conjunctival fat is continuous with the orbital fat. These are pseudolipomas. They present a herniation of orbital fat through the Tenon's capsule and can be confused with lesions such as lacrimal gland tumours, lymphoid tumours and lipodermoids. [2, 30] True lipomas occur in non-obese people. Histologically they are composed of lobules of fat held together by a connective tissue stroma and more or less encapsulated. [2]

Occasionally amyloid may be deposited in the conjunctiva constituting a type of primary amyloidosis which is rarely associated with systemic variety of the disease. [30] Clinically they are unilateral or bilateral, solitary or multiple, firm, rubbery, waxy-appearing, painless fusiform or polypoid elevations. [31]

In some cases the conjunctiva is diffusely thickened and slightly hyperemic. Ptosis occurs when the deposits involve the upper tarsal conjunctiva or the levator muscle. [32]

BENIGN VASCULAR TUMOURS:

Telangiectasias and lymphangiectasias:

These are irreversible dilatations of the pre existing blood and lymphatic vessels respectively as a consequence of local irritation or prolonged inflammation. They may be isolated or occur in the context of more complex syndromes such as thyroid ophthalmopathy where they arise at the insertion of recti muscles.

In Rendu-Osler disease which has an autosomal dominant mode of transmission, conjunctival telangiectasias are associated with those of the skin and mucosae of the nose, mouth, lungs and intestinal tract. In ataxia-telangiectasia (Louis-Bar

syndrome) an autosomal recessive condition, cerebella ataxia and ocular movement disorder precede the appearance of cutaneous and conjunctival telangiectasias. [25]

Haemangiomas:

These are proliferations of new blood vessels. They can be classified into capillary haemangiomas (strawberry marks) and cavernous haemangiomas. Capillary haemangiomas have their onset in infancy. They undergo rapid growth and spontaneous regression around the fifth year of life. They appear as red-bluish colored lesions that increase in size when the child cries. Cavernous haemangiomas differ from capillary ones by being located at a deeper site, arising during the second to fourth decade of life and by having a slow growth but without a tendency to spontaneous regression. If they arise in the orbit they may cause progressive exophthalmos.

Pyogenicum granuloma is a capillary haemangioma formed by proliferating capillaries and endothelial cells with an infiltrate of inflammatory cells. It appears as a lobe shaped, pedunculated or mushroom shaped red mass with smooth surface.

It develops in areas of previous trauma like following strabismus operation or excision of a bulbar conjunctival lesion without surgical re approximation of the epithelial margins (bare sclera technique). It may also develop in areas of previous inflammations such as chalazion or it may just arise spontaneously. [25, 23]

Another rare benign vascular conjunctival tumour is primary lymphoplasmocytoma. One case has been reported in Israel and five cases from other parts of the world. In all the six cases the disease remained limited to the conjunctiva and signs of systemic disease could be found after prolonged follow up. [33]

PIGMENTED LESIONS:

Benign acquired melanosis:

Benign acquired melanosis may be epithelial or sub epithelial in origin.

Epithelial lesions may be primary or secondary.

Primary acquired epithelial melanosis of the conjunctiva is a unilateral idiopathic melanotic pigmentation of the conjunctival epithelium presenting as a subtle yellow brown stippling within the epithelium. Usually begins in middle age or later and may involve any part of the conjunctiva. [23] Transformation to conjucntival melanoma is extremely rare and therefore biopsy of all primary acquired melanotic lesions is unwarranted as reported in the study done in USA. [34] Biopsy is recommended in widespread, large, thickened, dark, palpebral, unusually vascular or progressive lesions. [34]

Secondary acquired epithelial melanosis of the conjunctiva may follow radiation, chemical injury (such as arsenic), Addison's disease and in chronic disorders of the conjunctiva (like trachoma, vernal conjunctivitis, onchocerciasis and keratomalacia).[13] They are typically unilateral, commonly in middle age or later life appearing anywhere in the conjucntiva. [24]

Histologically there is excess of melanin in the conjunctival epithelium. This is often confined to the basal cells but sometimes spreads into the overlying prickle cells. In some instances a minor degree of junctional proliferation can be seen. [24]

Sub epithelial acquired benign melanosis occur in association with melanosis bulbi or the nevus of Ota. These lesions develop in dark pigmented subjects appearing as thin conjunctival pigmentation which is light brown, interpalpebral, bilateral and asymptomatic without risk of malignant transformation. [13]

Pigmented naevi:

Although these harmatomas have an embryonic basis, they may not be clinically apparent at birth. [2] They are the most common pigmented lesions in the conjunctiva and skin. Histologically they are made up of groups of small cells with a deeply staining nucleus and a scanty cytoplasm. Epitheloid naevus cells are found particularly in superficial sub epithelial tissue which are large cells with abundant eosinophillic cytoplasm with prominent nucleoli forming a stage in the evolution of the classical naevus cells. [2] Cystic epithelial down growth may occur. [25] Although not often clinically distinguishable, four types can be differentiated depending on the location of these cells. [2]

Junctional naevi:

In this type cells are confined for the most part to the basal layer of the epithelium. They may spread to the sub epithelial tissue or become malignant. Clinically they are flat or slightly elevated lesions.

Sub epithelial (Intramucosal) naevi:

In this type of naevi cells are confined to the sub epithelial tissue and the epithelial layer shows no junctional activity. Clinically they are elevated constituting the common mole of the skin and never undergoes malignant transformation.

Compound naevi:

These have both junctional and sub epithelial elements. They tend to be elevated and because of the junctional element they are capable of carcinomatous change though relatively rarely.

The blue naevi:

Situated in the dermis, are made up of spindle cells resembling those of neurofibroma.Cells do not show significant anaplasia and malignant change does not occur in the conjunctiva.

As far as malignant transformation is concerned in the two types with junctional elements (junctional and compound naevi), it is a very rare occasion. [24, 23, 2, 25, 35]

Inflamed juvenile conjunctival naevi (IJCN) are often erroneously suspected to be malignant because of their rapid growth. A study done in Israel to characterize IJCN clinically and pathologically showed absence of malignant features in the specimens studied. A total of 63 inflamed naevi where resected and 25% showed simple compound conjunctival naevi on histological studying. The other 75% showed compound naevi with prominent inflammatory features (discrete lymphocyte aggregates, plasma cells and eosinophils). There was a history of allergic disease in 75% of patients whose specimens showed inflammatory features. [36]

Increased melanogenesis can also result from pituitary stimulation (pregnancy, adrenal insufficiency) physical irritation, actinic radiation, inflammation and coexisting malignant melanoma. [2, 25]

PERIPHERAL NERVE TUMOURS:

Neurofibromas and neurilemomas are benign peripheral nerve tumours originating from connective tissue cells of the supporting tissues of the nerves or from the cells of the sheaths of Schwann or from both. The exact nature of the parent tissue is frequently difficult to determine. Many occur with multiple neurofibromatosis (Von Recklinghansen's disease) but a solitary growth may appear on the outer eye as an

isolated phenomena. Histology shows strands of elongated cells forming an interlacing network with palisading of the nuclei. [2]

INFLAMMATORY CONJUNCTIVAL GROWTHS:

A diffuse or focal granulomatous inflammatory reaction to irritation, ulceration or injury may arise from any part of the conjunctiva. Common causes are a retained foreign body such as an eyelash, bristle of a brush, a stone or a talc particle, a grain of corn or other vegetable matter. [2] This reaction may also be due to certain bacteria (mycobacterium in particular), mycotic organisms (coccidioidomycosis), parasites and some unknown factors (sarcoid, rheumatoid nodule). [25]

Clinically they may be sessile or polypoid in which case when strangulated they may drop off or may resemble a blood cyst. When highly vascularized the surface may bleed producing a condition of blood tears and if they become ulcerated the condition may resemble a malignant growth. Histologically they are composed of typical granulation tissue with its great variety of individual elements, young connective tissue cells, leucocytes, giant cells, endothelial cells and thin newly formed blood vessels.

In children and young adults allergic granulomatous nodules may grow beneath the epithelium of the conjunctiva. Histologically they show giant cell and eosinophollic granulomatous reaction to an antigen antibody precipitate in relation to parasite or fungi. Rarely fragments of nematode larvae can be found but usually no foreign bodies or parasites are identified in the lesions.

In the absence of surgical intervention these lesions can disappear spontaneously or after corticosteroid therapy in a few weeks or months. [37]

Epithelium may cover the mass in the periphery and may deep in the crevices of the granulation tissue, an appearance that should not be mistaken for the infiltrating process of a carcinoma. Diagnosis is confirmed by histology. A number of eyes have been enucleated under the impression that the growth was malignant. [2]

An unusual epibulbar inflammatory process has been reported in a patient with HIV. The lesion has been treated as conjunctivitis for sometime and later on an excisional biopsy showed inflammatory cells including eosinophillic abscess which illustrates the occurrence of epibulbar allergic granulomatous nodules in a HIV positive patient. [38]

Conjunctiva plasmoma is an inflammatory granulomata consisting of plasma cells representing a tissue reaction to chronic irritation like trachoma.

The hyperplasia is sometimes diffuse and occasionally it is extensive and limited to give the clinical appearance of a tumour. Usually it appears on the conjunctiva of the upper lid, occasionally at the inner angle and the bulbar conjunctiva or on a part of cornea affected by pannus. Histologically the mass is composed of plasma cells distinguished from neoplastic cells by their maturity together with macrophages.

Hyaline degeneration is common. Some cases show a regular conformation of hyaline spheres (Russell Bodies) the presence of which confirms a granulomatous nature. [2]

CONJUNCTIVAL DEGENERATIONS:

Pingueculae

Pingueculae are localized, yellowish-gray elevated masses close to the limbus on the nasal or temporal side or both of the cornea in the interpalpebral part of the bulbar conjunctiva. [23, 1, 24]

More often occurs nasally and develops into a triangular patch with it is base abutting against the cornea. As a rule it remains stationary at a moderate size but may develop and become quite conspicuous especially when the eye is injected and it is avascularity make it stand out with startling prominence.

Their location in the interpalpebral zone, their absence in infancy and young children and their more frequent occurrence in older individuals living in areas with high levels of sunlight suggest that they are degenerative lesions causally related to prolonged actinic exposure. [23] Wind and dust have also been reported to play a role in the aetiology. [1, 35]

A study was done in Australia to describe the prevalence of pterygia and pinguecula in an older population. Associations with skin, hair and eye color, skin sun sensitivity, sun related skin damage and skin cancer was also examined. Results showed a slight age related increase in prevalence for both lesions. The study also found significant associations between the two conjunctival degenerations and increased skin and hair pigmentation, decreased skin sun sensitivity and sun related skin damage. [39]

Another study was done in Taiwan to investigate outdoor hazards and their relationship to conjunctival disorders experienced by postmen. The study showed that the outdoor nature of postal work was significantly associated with the

occurrence of pingueculae as well as pterygium ($P<0.05$). This is explained by an increase in the cumulative occupational sunlight exposure (an increase by one unit-one year x hour/day) increases the risk of developing pingueculae and pterygia by 2.1% and 0.8% respectively. [40]

Pingueculae and pterygia fluoresce in UV light a property that serves to distinguish them from malignant epitheliomata.

Occasionally it may become inflamed in which case the epithelium is thickened resembling leukoplakic areas in appearance and in more severe cases intraepithelial abscesses may develop. [1]

Histologically the essential changes are in the substantia propria where collagen fibers become fragmented, curled and more basophilic with hematoxylin–eosin stain. The fibers also stain with elastic tissue stains but are not elastic in nature and are insensitive to treatment with elastase (elastase does not prevent positive staining for elastin).

This is the reason why this particular kind of collagen degeneration is referred to as elastoid or elastotic degeneration. [35] Deposition of amorphous hyaline material may also occur.

Two cases of pingueculae have been reported to have occurred during the course of Sjogren's syndrome in France. [41]

Clusters of Gaucher cells in the conjunctiva as it occurs in Gaucher's disease may also present as pingueculae. [42]

Pterygia

A pterygium (wing) is a wedge of conjunctival tissue that grows across the limbus into the superficial cornea in the interpalpebral fissure most commonly on the nasal

side. It is often preceded by a pinguecula. [24] Although the pathogenesis is not fully understood, it is probable that drying of the interpalpebral tear film as it occurs in low atmospheric humidity and exposure to constant wind is an initiating factor. Drying of the interpalpebral tear film occurs most readily in the medial one third of the interpalpebral fissure because this part is farthest from the lacrimal glands and nearest to the puncta and also when eyes are partially closed against glare or wind this part remains relatively more exposed than the lateral one third. This drying exposes the peripheral corneal epithelium; Bowman's membrane and underlying stroma to the destructive effects of the ultraviolet light reflected from water, sand or snow. The tissue damage sustained stimulates the advance of limbal vessels and fibroblasts into the cornea.

The vascularization is hastened by factors such as chronic infection or dust. With increased conjunctival vascularity organization of this fibrovascular tissue causes traction that draws the characteristic wing of conjunctiva tissue on to the cornea.

In Barbados pterygia have been found to be almost twice as frequent among outdoor workers but only one fifth as likely among those who always use sunglasses outdoors. [43]

Similarly in Australia and Singapore pterygium is a significant public health problem in rural areas. This is primarily due to prolonged ocular sun exposure during outdoor

Activities. [44, 45]

The incidence of pterygia also varies with the duration and amount of exposure to these environmental factors (dry atmosphere and UV light) as evidenced by a study done in Taiwan. [40] In this study it was found that the risk of developing pinguecula

and pterygia is increased when the cumulative occupational sunlight exposure is increased. [40]

A high incidence of pterygium has also been reported among indoor sawmill workers suggesting that other factors may operate in some situations. [24, 2, 46]

A low penetrance autosomal dominant heredity has also an influence in the occurrence of pterygia. It is not the actual lesion which is transmitted but rather the tendency of the eye to react this way to environmental stimuli. [1]

Histologically a pterygium consists of fibrovascular tissue, the collagen fibers of which often exhibit elastosis. It is covered by conjunctival epithelium except at it is apex where avascular fibroblastic tissue can be seen growing into the cornea along cleavage planes between the epithelium, Bowman's membrane and stroma. Here it is covered by the corneal epithelium. Older pterygia become densely fibrous with areas of hyaline degeneration and sometimes-granular calcifications. [24]

Unexpected histological findings in pterygium have been reported in a case in Italy where an atypical grayish area on an apparently trivial pterygium convinced the surgeon to request histological examination. Results showed conjunctival intraepithelial neoplasia. The lesion was from a 53 years old white male who has been living in Kenya for 35 years. [47]

Occasionally a pseudopterygium grows which is a result of an inflammatory process.

A fold of inflamed conjunctiva becomes adherent to a progressive ulcer near the corneal margin being passively dragged across the limbus. The conjunctiva is adherent only at the apex forming a bridge over the limbus under which a probe can be passed. It may occur at any part of the corneal margin.

LESIONS WITH POSSIBLE MALIGNANT TRANSFORMATION (PRECANCEROUS LESIONS):

EPITHELIAL LESIONS:

Epithelial dysplasia:

Epithelial dysplasias are characterized by a thick and hyper cellular epithelium composed of abnormal cells arranged abnormally. The abnormal cells are found only in part of the epithelial thickness. Severity of the cellular abnormalities also ranges from mild to severe. Mild dysplasia is possibly reversible. Severe dysplasia begins to approximate to carcinoma in situ and the two conditions may coexist in the same lesion.

Actinic keratosis (Senile keratosis):

These clinically appear as keratotic plaques or pseudocarcinomatous hyperplasia but are often scaly due to adherent surface keratin. They develop slowly within the epithelium overlying a preexisting pinguecula or pterygium. As the name suggests prolonged ultraviolet light exposure is pathogenically related to these lesions.

Histologically, the degree of cellular atypia varies from mild (features of mild dysplasia) to severe pleomorphism and dyskeratosis with abnormal mitotic figures throughout all levels of the thickened epithelium (features more characteristic of severe dysplasia). Actinic keratosis is the commonest precursor of invasive squamous cell carcinoma of the conjunctiva.

Carcinoma in situ(Conjunctival Intraepithelial Neoplasia-CIN):

This presents clinically as a limbal plaque which is often well vascularized and is sometimes seen to be advancing into the corneal epithelium on a broad front.

Hyperkeratosis is minimal in amount so that the lesion appears opalescent rather than leukoplakic.

Familial factors like light hair and ocular pigmentation and environmental factors such as exposure to petroleum products and heavy cigarette smoking, may play a role in the development of CIN as evidenced by a case control study done in Philadelphia. [48] Histologically carcinoma in situ is characterized by total loss of normal cellular maturation affecting the full thickness of the epithelium.

The abnormal cells have large elongated hyperchromatic nuclei. The changes are confined to the epithelium the basal layer retains an intact basement membrane. Keratinized cells are relatively infrequent. Conspicuous mitotic activity of all layers and mitotic figures may be seen near the surface. [24]

All plaques showing carcinoma in situ must be scrutinized for micro invasion of underlying tissues that is seen as spiky irregular rootlets of malignant epithelium thrusting through the basement membrane into the stroma. This signifies the onset of invasive squamous cell carcinoma. [23, 24]

Carcinoma in situ sometimes masquerades as persistent keratoconjunctivitis that is unresponsive to treatment. Scrapings from the lesion stained by Papanicolaou or Giemsa stain may help to establish the correct diagnosis. [24]

In xeroderma pigmentosum the conjunctiva and cornea are often severely involved in the disease process exhibiting a spectrum of changes including pterygium-like growths and epithelial neoplasms (CIN and invasive squamous cell carcinoma).[23,49,50]

Each of the lesions in the precancerous group in their pure state can be identified histologically and differentiated from others. In this group however most lesions are

not uniform and different degrees of cellular atypia are frequently present in the same lesion therefore in assessing the sub classification of a given lesion the most severely affected areas have to be judged. [23]

A clinicopathological study of 45 cases was done in USA to characterize precancerous conjunctival intraepithelial neoplastic lesions basing on the degree of parakeratosis, hyperkeratosis and atypia. Of the 45 cases studied, 24 were classified as actinic keratosis and 21 cases as dysplasia. One patient with dysplasia had numerous recurrences and locally invasive squamous cell carcinoma developed. [51]

In Australia the incidence of histologically proven dysplasia, carcinoma in situ and invasive carcinoma of the cornea and conjunctiva is estimated to be 1.9 per 100,000 per year. This figure is averaged for 10 years as reported in a survey done nearly 10 years ago. [52]

Pigmented lesions:

As pointed out previously, the two types of naevi capable of malignant transformation are junctional and compound naevi. However this is a relatively rare occasion. Primary acquired melanosis with cellular atypia also has a potential for malignant transformation.

MALIGNANT CONJUNCTIVAL GROWTHS:

Malignant conjunctival growths may arise primarily in the conjunctiva or secondarily by extension from adjacent or remote sites of diseases. [25]

Primary malignant conjunctival growths:

Generally the most common primary malignant conjunctival tumour is squamous cell carcinoma (including conjunctival intraepithelial neoplasia). Others are malignant melanoma and B-cell nonHodgkin's lymphoma. [16] Kaposi's sarcoma of the conjunctiva has also been found to be on the increase in recent years. In a study done in Uganda to assess the trend of cancer incidence over a period of 38 years (1960-1997), an increase in the incidence of most cancers was revealed including squamous cell carcinoma and Kaposi's sarcoma of the conjunctiva. [17]

Epithelial lesions:

These are characterized by the capacity of deep invasion across the basement membrane and of rarely metastasizing even to lymph nodes and they are seldom lethal. Four forms of epithelial lesions can be distinguished

1.Squamous cell carcinoma

2.Basal cell carcinoma

3.Mucoepidermoid carcinoma

4.Spindle cell carcinoma

Squamous cell carcinoma

Squamous cell carcinoma develops at the limbus in the interpalpebral fissure initially appearing as a small, gray raised patch resembling a phlycten. [2]

As far as aetiology is concerned, exposure to ultraviolet light has been reported to be a major risk factor in the development of squamous cell carcinoma of the conjunctiva. [53, 54, 55] Other aetiological factors for squamous cell carcinoma are infection by HPV type 16 and HIV. [17]

Poorly fitting ocular prosthesis following enucleation has also been reported to cause development of squamous cell carcinoma after some years. Histological studying of two cases was done in USA and in one case the tumour was found to be metastatic to the parotid gland. [56]

Squamous cell carcinoma of the conjunctiva may arise directly as squamous cell carcinoma or as a transformation of a conjunctival intraepithelial neoplasia.

As the tumour grows two morphological variants can be described, the diffuse and the nodular variant. The diffuse variant may have a sessile gelatinous or leukoplakic appearance, highly vascularized masquerading as chronic conjunctivitis. Tumour thickening occurs late thus making it difficult to diagnose. A conjunctival biopsy is therefore recommended in cases of conjunctivitis lasting more than three months.

The nodular lesion is a circumscribed papillary or warty growth rapidly growing and exhibits an increased metastatic potential.

Squamous cell carcinoma of the conjunctiva tend to be only superficially invasive and to have a relatively benign course.

Superficial extension occurs with tumour spreading to infiltrate the sub epithelial conjunctiva tissue and the superficial corneal stroma presenting as keratitis. [24]

The sclera presents a compact barrier to it's progress into the eye and if it does so it is a very rare occasion and typically occurs through the limbus presenting with iridocyclitis, neovascularization of the iris, peripheral anterior synechias and glaucoma. [57, 58]

Marked surface extension over the sclera results in tumour protrusion as a fungating mass between the lids. Orbital invasion carries the risk of spread into the sinuses and brain and is said to be the most common cause of death related to this tumour.

Beyond the eye and orbit metastases can be found in the regional lymphnodes, the lungs and bones. In one study were 27 cases were reviewed, three cases were found with deep corneal invasion, two with intraocular extension, four-showed orbital invasion and two exhibited spread to regional lymphnodes. One patient died from metastatic tumour. [59]

Histologically,most squamous cell carcinomas are well differentiated and often exhibit a surface keratinization.

Atypical epithelial cells proliferate downward breaking through the basement membrane to the stroma. Depending upon the degree of differentiation, there is great variation in the size and configuration of invading cells. One may encounter hyperplastic and hyperchromatic cells, individually keratinized cells, concentric collections of keratinized cells (horn pearls), loss of cellular cohesiveness and atypical mitotic figures.

Basal cell carcinoma:

This appears as a nodular, fleshy, vascularized and mobile lesion with no signs of surrounding inflammation. Commonly affecting elderly people it arises in the interpalpebral zone at the limbus on the nasal aspect.

Primary basal cell carcinoma of the conjunctiva occurs very rarely and has been noted to arise from trachomatous pannus but has also occurred in the palpebral conjunctiva.

Usually it is secondary to spreading of eyelid skin lesion to the conjunctiva.

Histologically it resembles squamous cell carcinoma differing from it by cellular changes involving the deeper cell layers. It may take on several appearances: solid

masses of uniform cells with basophilic nuclei, peripheral palisading of basal cells, or strands or cords of cells that appear in an "Indian file" pattern. [60]

Mucoepidermoid carcinoma:

This is a malignant epithelial tumour composed of varying proportions of mucus secreting cells, squamous cells and intermediate cells (basal cells).

Usually it is a rare tumour localized at the limbus but most invasive with a rapid infiltration of the orbit and the possibility of metastases through the lymphatics. It involves mostly elderly individuals in the 7th decade of life. [61, 62, 63]

Histology shows an epidermoid component characterized by numerous cornified epithelial pearls and a mucoproductive one. The two components can be combined in various ways. Mucin production may be found in only a small portion of the tumour and in some cases mucin is not found in the original lesion but in the recurrent lesion. [23]

Spindle cell carcinoma:

This variant of malignant epithelial tumour is occasionally encountered in the conjunctiva. [64] Histologically it shows spindle cells with hyperchromatic nucleus and many desmosomes forming fascicles that resemble a sarcoma. [23] This lesion has a remarkable capacity of infiltration invading the limbus and the deeper ocular tissues.

A case has been reported which showed recurrence and displayed invasion of the limbal tissues with extension into the trabecular meshwork. [64]

Pigmented lesions:

Malignant melanoma

This is a relatively rare tumour that may develop in a preexisting benign naevus having a junctional component or in area of precancerous melanosis or without any antecedent lesion. [24]

It is a unilateral malignancy primarily affecting middle aged whites. The annual average age adjusted incidence is reported to be 0.012 per 100,000 populations in USA. [65] In Sweden the annual incidence during a 22.5-year period (1969 to mid 1991) was found to be 0.0240 per 100,000. [66]

Although it is rare in the black population, primary acquired melanosis, which may be difficult to differentiate from racial melanosis clinically and histopathologically in blacks, may lead to the development of melanoma. [67, 65]

The role of sun exposure in the development of conjunctival melanoma and other ocular melanomas involving the iris, ciliary body and choroid is still unclear. [68]

Epithelial conjunctival tumours may be pigmented and resemble melanoma but without any evidence of conjunctival acquired melanosis.

Two such lesions have been reported in a review of 60 conjunctival tumours. The two tumours were histologically pigmented papilloma and squamous cell carcinoma. [69]

Haemosiderin and foreign bodies can cause pigmentation of the conjunctiva and may on occasion suggest a naevus or melanoma. [24] Clusters of Gaucher cells (lipid laden macrophages) in Gauchers disease presenting as pinguecula may also suggest a melanoma. [42]

Clinically malignant melanoma starts developing as a very small lesion that with time become raised, lobulated or nodular. Eventually a large epibulbar tumour develops occasionally extending over the entire conjunctival sac and filling fornices, the cornea covered and the globe hidden in neoplastic tissue. Depending on the presence or absence of pigment, the tumour is black, brown or pinkish red. Pigmented lesions are 5 times more common than the non-pigmented ones. The presence of pigment is not a manifestation of malignancy. [2]

Histologically in at least 50% of cases there is no evidence of preceding lesion either because there never was one or because all trace of it has been obliterated by the melanoma. [24] Two contrasting pictures may therefore be seen.

In early tumours and in well-established tumours derived from naevi, anaplastic changes are seen in the junctional zone of the epithelium. Cells are large, rounder and separate themselves from each other showing variation in size, shape and chromatin pattern of the nuclei. The nucleoli are large or multiple with abnormal mitotic activity and the cytoplasm shows vacuolation and hyperpigmentation. The degree of malignancy can be assessed by the extent of proliferative activity and anaplasia that occurs in this layer.

The sub epithelial tissues are freely invaded showing features similar to the one seen in benign lesions. However great karyokinetic activity and nuclear irregularity is also observed.

In the other more established cases no evidence of naevoid origin can be traced and the tumour mass is made up of irregular, polygonal and spindle shaped cells which have invaded the sub epithelial tissues. In the majority of cases a sub epithelial infiltration of inflammatory cells is evident.

A few number of patients with melanoma developing from precancerous melanosis suffer metastatic death and this is often delayed for many years after the first appearance of the melanoma. [24]

In one study the prognosis was closely related to the subsite and size of the primary tumour. Metastatic spread was very uncommon in patients with melanomas less than 1.5mm in maximum thickness, but the outcome of the disease in patients with tumours greater than 1.5mm was not always bad. [70]

Lymphomas:

Primary simple conjunctival lymphomas occur without evidence of a systemic disease.

They are frequently bilateral and often symmetrical most commonly found in middle-aged adults.

Clinically they appear as small, hard, red and fleshy tumours quite painless and of slow growth involving any part of the palpebral or bulbar conjunctiva. Although they may become invasive many years after the first appearance, the general prognosis is usually good.

However, in a report of clinical course and pathologic features of 6 cases of primary conjunctival non-Hodgkin's lymphoma (NHL) from Netherlands, the disease developed within a short period of time to stage IV and the response to therapy was poor. [71] This revealed a worse prognosis than would be expected according to the histopathologic classification. Four of the six patients died of NHL, three of them within 15 months.

Histologically they show small lymphocytes with irregular nuclei and abundant cytoplasm, variable degrees of differentiation, infiltration of reactive follicles and infiltration of epithelial structures.

The most common type encountered in the conjunctiva is B-cell nonHodgkin's lymphoma. [16]

Kaposi's sarcoma (KS):

Kaposi's sarcoma (multiple haemorrhagic idiopathic sarcoma) is a malignant mixed vascular tumour of skin and mucous membranes. [25]

In the past KS of the conjunctiva was considered to be a rare disease primarily occurring in older individuals who have similar lesions of the skin of the legs. [72, 73] This tumour has now been observed in the conjunctiva of young individuals afflicted with an acquired immunodeficiency syndrome. [74, 75] It is said to affect about 25% of patients with AIDS. [76]

Clinically it appears as a tender circumscribed sub epithelial, bright red nodule or diffuse elevation most often in the palpebral or lower fornicial conjunctiva. [23] It may resemble a foreign body granuloma or cavernous haemangioma. [76]

KS has been found to mimic subconjunctival haemorrhage and atypical hordeolum in HIV infected individuals. [77]

In one study 20% of HIV patients with KS were found to have eyelid and conjunctival lesions resembling chalazion and sub conjunctival haemorrhage. [78] KS has also been observed in the conjunctiva of a patient with myasthenia gravis. [79]

Histology shows spindle shaped cells with elongated oval nuclei, well formed capillary channels and vascular slits containing blood but no definite endothelial

lining. [23, 2, 80] Sometimes the disease is associated with malignant lymphoma with a very poor prognosis. [25]

Leiomyosarcoma:

This is a malignant tumour of smooth muscle cells commonly arises in the uterus and gastrointestinal tract. [81]

Within the ophthalmic literature it has been reported rarely in the orbit. [82] One case of conjunctival leiomyosarcoma is reported. [83] The lesion presented as an inflamed pterygium that was initially treated with topical steroids. A few months later a white nodule developed at the limbus and biopsy revealed a squamous cell carcinoma. Twenty years later he presented with masses at the limbus (both temporal and nasal) associated with corneal stromal oedema and scarring. He underwent penetrating keratoplasty and biopsy of the limbal lesions showed a malignant spindle cell tumour. Another previously reported case was of a 20 years lady with xeroderma pigmentosum. [84] This patient also had numerous cutaneous squamous cell carcinoma, basal cell carcinoma as well as melanoma lesions. A limbal tumour initially believed to be a leiomyoma on biopsy recurred rapidly and exenteration showed a mesenchymal malignancy, probably a leiomyosarcoma.

Secondary malignant conjunctival tumours:

The conjunctiva may also be invaded by adjacent, remote and systemic neoplasia. Lesions from adjacent structures may originate in the eyelid, nasolacrimal passages, eyeball, orbit or the sinuses.

Basal cell carcinoma may extend to the conjunctiva from the eyelid skin and this is the common origin of basal cell carcinoma of the conjunctiva.

Orbital rhabdomyosarcoma of children may extend to the conjunctiva and make its first clinical appearance in this location. Melanomas from the ciliary body, skin or mucous membrane anywhere in the body may extend to the conjunctiva.

Remote sites of primary malignancy with metastasis to the conjunctiva have also been documented. In USA a report of 10 cases with metastatic tumours to the conjunctiva revealed the primary malignancy to be carcinoma of the breast in 4 patients, lung cancer in 2 patients, laryngeal carcinoma in 1 patient, cutaneous melanoma in 2 patients and unknown in one patient. [85]

Systemic diseases like leukemia and lymphoma may also manifest with infiltrates in the conjunctiva. A case of bilateral conjunctival tumours as a first sign of relapse of acute monoblastc leukemia has been reported in Hong Kong. [86] The tumours appeared as pink raised painless lesions in the upper conjunctiva. Biopsy revealed a dense mononuclear infiltration.

Lymphomas occurring with a generalized blood disease may also present with conjunctival infiltrates. There is also enlargement of lymphnodes, spleen and liver and changes in bone marrow as manifestation of a systemic disease. The clinical presentation and histological picture resembles that of primary conjunctival lymphoma.

One study done in USA revealed that 31% of patients with conjunctival lymphoid tumours more often involving the fornicial or bulbar conjunctiva and those with multiple conjunctival tumours are associated with systemic lymphoma. [87] Related systemic lymphoma can manifest many years later therefore long-term follow up is advised. The ultimate prognosis is usually bad.

Lymphosarcoma is a highly malignant but rare tumour of the conjunctiva that occurs as a localized manifestation of a generalized lymphosarcomatous process affecting lymphonodes widely throughout the body. They grow rapidly showing a high local malignancy and a special tendency to spread by lymphatics. Histologically they resemble simple lymphomas.

CONJUNCTIVAL TUMOURS ASSOCIATED WITH HIV INFECTION.

Ocular disease is often the presenting symptom in an HIV infected individual. [88] Conjunctival growths fall in the category of neoplasms of the eye and adnexa as ocular manifestation of HIV infection.

Conjunctival neoplasms reported to be highly prevalent in individuals infected with HIV are squamous cell carcinoma, B-cell non-Hodgkin's lymphoma and Kaposi's sarcoma. [3, 4, 6, 16, 17, 18, 19, 20]

In Tanzania, a study conducted at Muhimbili Medical Centre on ocular manifestations in children with HIV infection showed a prevalence of 38 percent among HIV seropositive children. [89] Conjunctival lesions were the most common ocular manifestations.

Pathogenesis of HIV related neoplasms:

Human immunodeficiency virus is the primary aetiologic agent of acquired immunodeficiency syndrome. Human immunodeficiency viruses are retroviruses belonging to the lentivirinae family. Most human immunodeficiency viruses are variants of HIV-1. A second variant; HIV-2 seems to be prevalent only in West Africa and is much less virulent. [90, 91] Some subtypes of HIV-1 such as C, E and A appear to be transmitted more efficiently than HIV-1 B, which is the major subtype

in the United States and Europe. [91] The virus severely impairs cell-mediated immune response by infecting and killing T-lymphocytes. The virus selectively binds to the membrane of the helper T-cell (T4), the T4 surface antigen on these lymphocytes serving as the virus receptor. The CD4 molecule is the major receptor for HIV; it has high affinity for viral envelope. The cardinal feature of HIV infection is the depletion of T helper inducer lymphocytes.

The immunosuppressive effect of HIV is a major factor responsible for development of conjunctival tumours. [92]

Regarding Kaposi's sarcoma the HIV-1 Tat protein has been shown to have angiogenic property in animal models and to stimulate the growth of KS spindle cells in vitro. [92] This may therefore be a factor for the development of KS lesions. In addition, increased cytokine levels found in AIDS patients may be responsible for this effect. [92]

The production of these growth factors and the proliferation of spindle endothelial cells may be associated with an additional infectious agent. HHV-8 seems the best candidate reported so far but it is role in the pathogenesis of KS remains to be clarified.

The role of HIV-1 in the development of non-Hodgkin's lymphoma seems to be indirect and related to an effect of HIV immunoregulation. [92] Several host factors such as disrupted immunosurveillance, chronic antigen stimulation and cytokine dysregulation play a role in the lymphoma pathogenesis in HIV-1 infected individuals.

Squamous cell carcinoma is said to develop from the immunosuppressive effect of HIV-1 infection, which may promote the development of HPV-related precancerous lesions. HIV-1 also enhances the development of these squamous cell carcinoma precancerous lesions. [92]

A number of studies have been done on the epidemiology of AIDS related malignances.

In USA it has been found that AIDS results in an extraordinary increase in the risk of two malignances: KS and B-cell non-Hodgkin's lymphoma (KS relative risk>10,000 and B-cell non-Hodgkin's lymphoma relative risk>100). [18]

Trends in cancer incidence in Uganda spanning 38 years in total (1960-1997) have showed a marked increase in incidence in most cancers the only exceptions being cancers of bladder and penis. [17] The study period coincides with the marked social and lifestyle changes overshadowed by the dramatic effects of AIDS epidemic. KS emerged as the most common cancer in both sexes in 1990's and a large increase in incidence of squamous cell carcinoma as well as that of NHL has also been noted.

Conjunctival squamous cell carcinoma has been studied in a number of African countries during this AIDS epidemic period and the results seem to be similar. In Tanzania a retrospective analysis of records from the Tanzania pathology department serving north and central Tanzania from 1976 to 1997 was done. The analysis also included cases of conjunctival squamous cell carcinoma presenting in the twenty-two years of study. Results showed a rise in the incidence of conjunctival squamous cell carcinoma in the last three years of study (1995-1997). [4] Only 5 patients had been tested for HIV status and of these four were seropositive.

A six-fold increase in the incidence of conjunctival squamous cell carcinoma has been reported in Uganda (6 per million per year from 1970 until 1988 to 35 per million per year in 1992). [3] Seventy five percent of 48 patients with conjunctival tumours seen at the ophthalmology clinic were HIV seropositive compared to the 19% seropositivity rate among 48 matched controls. Other factors that may contribute to the high incidence of these tumours in equatorial Africa like exposure to ultraviolet light, conjunctival papilloma virus infection and chronic conjunctival disease should not be forgotten. In another study done in Uganda, a ten-fold increase in the risk of conjunctival squamous cell carcinoma in HIV infected individuals has been reported. [89] Patients were tested for antibodies to HIV, HPV type 16, 18, and 45. The seroprevalences for antibodies against HPV-18 and 45 were too low to make reliable conclusions. The presence of anti HPV-16 was not significantly associated with squamous cell carcinoma of the conjunctiva. The risk of this cancer was increased with increased time spent in cultivation and therefore in direct sunlight suggesting exposure to ultraviolet rays.

Another study done in Uganda and Malawi revealed a strong association between HIV infection and conjunctival squamous cell carcinoma. [93] In Uganda conjunctival biopsies were also tested for HPV-16 by polymerase chain reaction (PCR) and 35% of carcinoma samples were positive for HPV-16.

In Congo, a review of 10 AIDS patients with biopsy confirmed conjunctival squamous cell carcinoma and CIN was done to determine the clinical characteristics.[5] Results showed similar features as those reported in immunocompetent individuals but in AIDS patients these tumours were noted to be occurring in a younger age group and are more aggressive.

Kaposis sarcoma is a common malignancy in AIDS patients which can also involve the conjunctiva. One hundred male homosexuals with AIDS related KS were examined prospectively for ophthalmic involvement. Of the 20 patients found to have ophthalmic involvement, 13 had only eyelid lesions, 4 had only conjucntival lesions and 3 had both eyelid and conjunctival involvement. [20] KS in patients with AIDS is said to be very aggressive and less responsive to treatment. [19]

An unusual epibulbar inflammatory process has been reported in a HIV positive patient. [38] The patient developed fleshy epibulbar nodules on the conjunctiva and cornea after being treated for conjunctivitis. A biopsy of the lesion was done which showed inflammatory cells including eosinophilic abscess illustrates the occurrence of epibulbar allergic granulomatous nodules in an HIV positive patient.

DIAGNOSIS OF ACQUIRED CONJUNCTIVAL GROWTHS

The clinical difference between the different histological types of conjunctival growths is frequently vague and therefore a definitive diagnosis is reached after histological examination.

A case has been reported in Italy, which showed unexpected histological findings in an apparently trivial pterygium. Biopsy disclosed presence of a conjunctival intraepithelial neoplasia. [47]

On the other hand clinically malignant growths may show benign features microscopically. Histopathological examination of a recent painless epibulbar growth located in the temporal conjunctiva in a 31-year-old male revealed a conjunctival myxoma. [29] A few malignant tumours like rhabdomyosarcoma may have similar clinical appearance.

Specimens for histology are obtained by taking an incisional or excisional biopsy. Excision of a lesion for histological examination also serves the purpose of treatment.

TREATMENT OF ACQUIRED CONJUNCTIVAL GROWTHS

Several treatment options are available for the different histological types of conjunctival growths. These include surgery, cauterization, cryotherapy, chemotherapy and irradiation.

Surgery may involve simple removal of the tumour only leaving the eyeball intact or an extensive procedure such as enucleation or exenteration depending on the tumour size and extension. Intraoperatively cauterization, cryotherapy and chemotherapy can be done to prevent tumour recurrence.

STUDY RATIONALE AND STATEMENT OF THE PROBLEM.

There is no recent data available for Tanzania on conjunctival growths. Several studies done in African countries over the past few years, have shown an increase in the number of patients with this health problem. [3, 4, 5, 17] A significant association with HIV infection has been reported. This study was done to describe the histological pattern of these growths and to correlate it to the HIV serological status. The results will help as a baseline data for further studies in the future.

Broad objective:

To describe the histological pattern of acquired conjunctival growths and correlate it to the HIV serological status of patients at MNH, Dar es salaam.

Specific objectives:

1.To describe the age and sex distribution of patients with acquired conjunctival growths as seen at MNH.

2.To determine the histological types of acquired conjunctival growths as seen at MNH.

3.To determine the proportion of patients with malignant growths among those with calcification in the conjunctival growth as seen at MNH.

4.To determine the proportion of patients who are HIV seropositive among those with malignant conjunctival growths and among those with benign conjunctival growths as seen at MNH.

MATERIALS AND METHODS:

Study design:

A cross sectional descriptive study on histological pattern of acquired conjunctival growths and their relationship to HIV infection was conducted at Muhimbili National Hospital from May 2002 to December 2002.

A total of 120 patients with acquired conjunctival growths were studied.

The sample size was calculated by the formula given below:

$N=Z^2 P (1-P)/D^2$

Where N=Number of subjects required

Z=95% confidence level (Z-score 1.96)

P=7.9%, estimated proportion of subjects with the disease (incidence of malignant lesions in a study done in Japan)

1-P=Estimated proportion of subjects without the disease

D=Desired precision (marginal error) 0.05

Case selection:

Consecutive patients with acquired conjunctival growths attending the MNH eye department during the period of study were included.

Data collection:

Consent for participation

An informed consent was obtained from every patient before recruiting him or her in the study. In case of children this was obtained from their parents. The consent form included the following information; the purpose of the study, the benefits of participation- undergoing surgery as part of treatment and the costs for participation.

For those who consented, counseling for HIV screening was also done as recommended by the National AIDS Control Program of the Ministry of Health. Patients who did not consent where excluded from the study. A consent form was then attached to the data sheet for each study subject.

Data sheet:

Basic information:

For each patient a data sheet was filled on which the following were recorded;

Serial number, date of examination, name, age, sex, address and involved eye. The best corrected visual acuity was assessed using a Snellen's / illiterate E chart for each eye.

Description of a conjunctival growth:

With the aid of a torch and slit lamp and a direct ophthalmoscope, description of a growth was recorded by its color, location, size, extension and presence of calcification. The rest of the eye was thoroughly examined. The type of surgery to be done for biopsy was determined and it was recorded on the data sheet.

Collection of specimens for biopsy:

Counseling for surgery was done depending on the type of surgery determined after examination. Specimens were obtained by taking incisional or excisional biopsies, enucleation of the eye or exenteration of the orbit.

Formalin 10% was used for preserving the specimens before they were sent to the central pathological laboratory for processing and histopathological examination.

Laboratory investigations:

Histopathological examination:

Processing of specimens was done first by embedding them in paraffin. Tissue sections of 5 microns thickness were then made and stained with haematoxylin and eosine histological stains.

Slides were examined under a light microscope by the author and a pathologist starting by tissue scanning with x 4 and x 10 magnification and then describing cellular details with x 40 magnification. Histological diagnosis of a conjunctival growth was given according to the microscopic cellular details obtained and was recorded on the data sheet.

HIV screening:

Blood samples for HIV screening were collected in vacutainers and sent to the virology laboratory for enzyme immunoassays. Two standard Enzyme Linked Immunosorbernt Assays (ELISA) tests were done, the Wellcozyme HIV Recombinant test (MUREX) and the Enzygonost Anti-HIV ½ Plus test (Behring). A sample was considered reactive (that is HIV positive) if positive on both ELISAs. Results of HIV screening tests were recorded on the data sheet.

Data analysis:

Data were analyzed using the EPINFO 6 package designed for population surveys in cross sectional studies.

RESULTS:

Description of the study population.

A total of one hundred and twenty patients with conjunctival growths were studied. Ninety-five (79.2%) patients were in the age range of 16-45 years. The minimum age was 8 years and the maximum age was 80 years. The mean age was 35.6 with a median of 35 years. There were 42(35%) males and 78(65%) females, giving a male to female ratio of 1:1.9 (Table 1).

Table 1: Distribution of the study population by age and sex.

Age (years)	Male		Female		Total	
	No	%	No	%	No	%
1-15	3	2.5	1	0.8	4	3.3
16-30	12	10.0	26	21.7	38	31.7
31-45	18	15.0	39	32.5	57	47.5
46-60	7	5.8	12	10.0	19	15.8
61+	2	1.7	0	0.0	2	1.7
Total	42	35.0	78	65.0	120	100.0

`Histological types of acquired conjunctival growths.

Most (85%) of the specimens were obtained by taking excisional biopsies of the lesions. Five percent of patients underwent destructive procedures (enucleation and exenteration) (Table 2).

Table 2: Types of surgery done for obtaining biopsy specimens.

Type of surgery	No	%
Excisional biopsy	102	85.0
Incisional biopsy	12	10.0
Enucleation	5	4.2
Exenteration	1	0.8
Total	120	100.0

Malignant lesions constituted 44.2%, while 11(9.2%) of the lesions were pre malignant. Benign lesions accounted for 46.6% of the lesions (Table 3).

Table 3: Distribution of the study population by histological group.

Histological group	No	%
Malignant	53	44.2
Pre malignant	11	9.2
Benign	56	46.6
Total	120	100.0

A total of thirteen histological types were obtained. Three types were malignant, 2 pre malignant and 8 types were histologically benign. Squamous cell carcinoma was the most common histological diagnosis amounting to 32.5% of all cases. Pterygia accounted for 24.2% and pingueculae accounted for 10.0%. Kaposis sarcoma was found to be prevalent by 10% (Table 4).

Table 4: Distribution of the study population by histological diagnosis.

Histological diagnosis	**No**	**%**
Squamous cell carcinoma	39	32.5
Pterygia	29	24.2
Pingueculae	12	10.0
Kaposis sarcoma	12	10.0
Dysplasia	7	5.8
Inflammatory (non specific)	6	5.0
Carcinoma in situ (CIN)	4	3.3
Papilloma	4	3.3
Malignant melanoma	2	1.7
Cyst	2	1.7
Candidiasis	1	0.8
Granuloma pyogenicum	1	0.8
Compound naevus	1	0.8
Total	120	100.0

Thirty-nine (73.6%) of all malignant lesions were squamous cell carcinoma. Kaposis sarcoma accounted for 12 (22.6%) lesions. Thirty-seven (69.8%) of patients with malignant growths were females. Kaposis sarcoma was equally distributed between the two sexes while females predominated (74.4%) among patients with squamous cell carcinoma. The proportion of females affected by squamous cell carcinoma among females with malignant conjunctival tumours was 78.4% while 10(62.5%) of males with malignant lesions were affected by squamous cell carcinoma (Table 5).

Table 5: Distribution of patients with malignant conjunctival growths by sex

Histological type	**Male**		**Female**		**Total**	
	No	**%**	**No**	**%**	**No**	**%**
Squamous cell carcinoma	10	25.6	29	74.4	39	73.6
Kaposis sarcoma	6	50.0	6	50.0	12	22.6
Malignant melanoma	0	0.0	2	100.0	2	3.8
Total	16	30.2	37	69.8	53	100.0

Dysplastic growths predominated among premalignant growths by 63.6%. There was an equal sex distribution between the two types of premalignant growths. (Table 6).

Table 6:Distribution of patients with premalignant conjunctival growths by sex

Histological type	Male		Female		Total	
	No	%	No	%	No	%
Dysplasia	4	57.1	3	42.9	7	63.6
Carcinoma in situ	2	50.0	2	50.0	4	36.4
Total	6	54.5	5	45.5	11	100.0

Among patients with pterygium 62.1% were females. Of those with pingueculae, females accounted for 75.0% (Table 7).

Table 7: Distribution of patients with benign conjunctival growths by sex

Histological diagnosis	Male		Female		Total	
	No	%	No	%	No	%
Pterygia	11	37.9	18	62.1	29	51.8
Pingueculae	3	25.0	9	75.0	12	21.4
Inflammatory	2	33.3	4	66.7	6	10.7
Papilloma	1	25.0	3	75.0	4	7.1
Cyst	1	50.0	1	50.0	2	3.6
Candidiasis	1	100.0	0	0.0	1	1.8
Granuloma pyogenicum	1	100.0	0	0.0	1	1.8
Compound naevus	0	0.0	1	100.0	1	1.8
Total	20	35.7	36	64.3	56	100.0

Forty-seven (88.7%) of all malignant lesions occurred in the age group 16-45 years. None of the patients in the age group 1-15 years had a malignant growth. Squamous cell carcinoma occurred in 72.3% of patients aged between 16 and 45. All patients with Kaposis sarcoma were also in the same age group (Table 8).

Table 8: Distribution of patients with malignant conjunctival growths by age.

Age group	Sq cell ca		KS		Mal Mel		Total	
	No	%	No	%	No	%	No	%
1-15	0	0.0	0	0.0	0	0.0	0	0.0
16-30	12	70.6	4	23.5	1	5.9	17	32.1
31-45	22	73.3	8	26.7	0	0.0	30	56.6
46-60	3	75.0	0	0.0	1	25.0	4	7.5
61+	2	100.0	0	0.0	0	0.0	2	3.8
Total	39	73.6	12	22.6	2	3.8	53	100.0

Sq cell ca = Squamous cell carcinoma, KS = Kaposi's sarcoma,

Mal Mel = Malignant melanoma

Five dysplastic lesions and 3 carcinoma in situ occurred in the age group 16 to 45 years accounting for 72.7% of all pre malignant lesions (Table 9).

Table 9: Distribution of patients with pre malignant conjunctival growths by age.

Age group	Dysplasia		Ca in situ		Total	
	No	%	No	%	No	%
1-15	0	0.0	0	0.0	0	0.0
16-30	4	57.1	3	42.9	7	63.6
31-45	1	100.0	0	0.0	1	9.1
46-60	1	50.0	1	50.0	2	18.2
61+	1	100.0	0	0.0	1	9.1
Total	7	63.6	4	36.4	11	100.0

Pterygia and pingueculae occurred in patients aged 16 to 60 years with pterygia predominating in the age group of 31 to 45 years (Table 10).

Table 10: Distribution of patients with benign conjunctival growths by age

Age grp	Pterygium		Pinguecular		Inflm		Papilloma		Cyst		Candidiasis		Granul pyogen		Cpd naevus		Total	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
1-15	0	0.0	0	0.0	0	0.0	2	50.0	1	25.0	0	0.0	1	25.0	0	0.0	4	7.1
16-30	8	57.1	5	35.7	1	7.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	14	25.0
31-45	14	56.0	5	20.0	3	12.0	2	8.0	0	0.0	0	0.0	0	0.0	1	4.0	25	44.6
46-60	7	53.8	2	15.4	2	15.4	0	0.0	1	7.7	1	7.7	0	0.0	0	0.0	13	23.3
61+	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	29	51.8	12	21.4	6	10.7	4	7.1	2	3.6	1	1.8	1	1.8	1	1.8	56	100.0

Inflm=Inflammatory, Granul pyogen=Granuloma pyogenicum, Cpd=compound

Presence of calcification in the growth:

Thirty-two (26.7%) of the conjunctival growths studied had calcification. Almost half (48.7%) of squamous cell carcinomas had calcification. In pterygia and pingueculae calcification was found to be present by only 20.7% and 8.3% respectively. However the differences were not statistically significant (P values =0.55 and 0.24 respectively) (Table 11).

Table 11:Distribution of the study population by histology and presence of calcification.

Histological diagnosis	Calcification +		Calcification -		Total	
	No	%	No	%	No	%
Squamous cell carcinoma	19	48.7	20	51.3	39	32.5
Carcinoma in situ	2	50.0	2	50.0	4	3.3
Dysplasia	3	42.9	4	57.1	7	5.8
Pterygium	6	20.7	23	79.3	29	24.2
Kaposi's sarcoma	0	0.0	12	100.0	12	10.0
Candidiasis	1	100.0	0	0.0	1	0.8
Compound naevus	0	0.0	1	100.0	1	0.8
Cyst	0	0.0	2	100.0	2	1.7
Granuloma pyogenicum	0	0.0	1	100.0	1	10.8
Inflammatory	0	0.0	6	100.0	6	5.0
Malignant melanoma	0	0.0	2	100.0	2	1.7
Papilloma	0	0.0	4	100.0	4	3.3
Pinguecular	1	8.3	11	91.7	12	10.0
Total	32	26.7	88	73.3	120	100.0

HIV serological status:

Fifty-one (42.5%) of the patients studied were HIV seropositive. Females accounted for 66.7% of these patients. However this difference was not statistically significant (P value 0.89) The proportion of HIV seropositive females was 43.6% while that of males was 40.5% (Table 12).

Table 12: Distribution of the study population by HIV status and sex.

Sex	HIV positive		HIV negative		Total	
	No	%	No	%	No	%
Female	34	43.6	44	56.4	78	65.0
Male	17	40.5	25	59.5	42	35.0
Total	51	42.5	69	57.5	120	100.0

None of the patients in the age group of 1-15 years was HIV seropositive. Twenty-seven (52.9%) of HIV positive patients were in the age group of 31-45 years with those in the age group 16-30 accounting for 39.2% of all HIV seropositive patients (Table 13).

Table 13: Distribution of the study population by HIV status and age.

Age group	HIV positive		HIV negative		Total	
	No	%	No	%	No	%
1-15	0	0.0	4	5.8	4	3.3
16-30	20	39.2	18	26.1	38	31.7
31-45	27	52.9	28	40.6	55	45.8
45-60	4	7.9	16	23.2	20	16.7
60+	0	0.0	3	4.3	3	2.5
Total	51	100.0	69	100.0	120	100.0

Most patients (74.4%)with squamous cell carcinoma were found to be HIV seropositive. This finding is statistically significant (P value<0.01). Only 13.8% of patients with pterygia were HIV seropositive. Kaposi's sarcoma was found to be significantly associated with HIV seropositivity (P value<0.01) (Table 14).

Table 14: Distribution of study population by histological diagnosis and HIV status

Histological diagnosis	HIV positive		HIV negative		Total	
	No	%	No	%	No	%
Squamous cell carcinoma	29	74.4	10	25.6	39	32.5
Pterygium	4	13.8	25	86.2	29	24.2
Kaposis sarcoma	11	91.7	1	8.3	12	10.0
Pinguecula	1	8.3	11	91.7	12	10.0
Inflammatory	0	0.0	6	100.0	6	5.0
Dysplasia	0	0.0	7	100.0	7	5.8
Carcinoma in situ	3	75.0	1	25.0	4	3.3
Papilloma	2	50.0	2	50.0	4	3.3
Malignant melanoma	0	0.0	2	100.0	2	1.7
Cyst	0	0.0	2	100.0	2	1.7
Candidiasis	1	100.0	0	0.0	1	0.8
Granuloma pyogenicum	0	0.0	1	100.0	1	0.8
Compound naevus	0	0.0	1	100.0	1	0.8
Total	51	42.5	69	57.5	120	100.0

Twenty-six (89.7%) of HIV seropositive patients with conjunctival squamous cell carcinoma were in the age group 16-45 years. The proportion of HIV seronegative patients with conjunctival squamous cell carcinoma who were in the age group 16-45 was 80% (Table 15).

Table 15: Distribution of patients with conjunctival squamous cell carcinoma by age and HIV serostatus.

Age	HIV positive		HIV negative		Total	
group	No	%	No	%	No	%
1-15	0	0.0	0	0.0	0	0.0
16-30	10	34.5	2	20.0	12	30.8
31-45	16	55.2	6	60.0	22	56.4
46-60	3	10.3	0	0.0	3	7.7
61+	0	0.0	2	20.0	2	5.1
Total	29	100.0	10	100.0	39	100.0

DISCUSSION

The epidemiology of tumour and tumour like lesions of the conjunctiva has been studied in several parts of the world. [14, 15, 94]

With the emergence of HIV/AIDS epidemic more studies have been done in African countries to associate these tumours with HIV infection. [3, 4, 17, 18, 19, 20]

Age and sex distribution.

In this study it has been shown that the age ranged from 8 years to 80 years with a mean age of 35.6 years. The majority of study subjects (79.2%) were in the age group of 16 to 45-years. 17.5% of study subjects were aged above 45 years. The age group 16 to 45 years includes active individuals who are at risk of exposure to factors that lead to the development of conjunctival tumours. These risk factors include outdoor activities that expose them to ultraviolet light rays and petroleum products, chronic conjunctival irritation, cigarette smoking, human papilloma virus and human immunodeficiency virus infection. [3, 4, 5, 6] In a similar study done in Japan, the age range of study subjects was found to be 47 to 92 years. [14] The younger age limit (16 years) at which conjunctival tumours occurred in this study as opposed to the study in Japan (47 years) may indicate a difference in aetiological or risk factors for these tumours. Our study has been done almost ten years after the Japan study. This time coincides with the establishment of the HIV/AIDS epidemic, which has severely affected sub-Saharan Africa. The adult prevalence rate of HIV/AIDS in sub-Saharan Africa by the end of the year 2002 is reported to be 8.8% compared to that of 0.1% in East Asia and Pacific. [21]

The role of HIV infection as one of the aetiological factors for the development of conjunctival tumours [3, 18, 93] and especially the early presentation of these tumours in HIV infected individuals [5, 6] explains this age distribution difference.
The younger age limit found in this study can possibly be explained by the tendency for old people in the African culture to take any ailment as part and parcel of the aging process and therefore they do not seek for medical attention.

In this study the male to female ratio of approximately 1:2 closely agrees with that of 4:6 found in the study in Japan. In both studies females predominated. This can be explained by the cosmetic awareness of females making them more likely to seek medical attention.

Histological types of conjunctival growths

In this study the histological pattern showed an almost equal predominance of malignant and benign growths while pre malignant growths accounted for the minority of cases (Table 3). The commonest histological diagnosis was squamous cell carcinoma while granuloma pyogenicum, candidiasis and compound naevus were the least common lesions (Table 4). This finding differs from that in Japan where pigmented nevi were the most frequent and mucinous carcinoma, sebaceous gland tumour and metastatic carcinoma were the least frequent. [14] In Germany the commonest growth was papilloma and the least common was a mucoepidermoid carcinoma. [94] Malignant growths were rare in Japan and Germany. Possibly the high prevalence of HIV infection in our study population which poses as one of the risk factors for malignant transformation can explain this. [92]

Furthermore in this study 10% of the growths were found to be Kaposi's sarcoma histologically. None of the growths studied in Japan and Germany were Kaposi's sarcoma. This tumour is one of the malignancies, which is highly associated with HIV infection. [18, 97]

Geographically, the risk of malignant transformation is reduced with increase in latitude. This is due to a reduced risk of exposure to dry atmosphere and ultraviolet light rays making those residing close to the Equator highly susceptible to malignant transformation. [95]

In this study, pterygium was the commonest among benign growths followed by pinguecula. This finding differs from that obtained in a community survey done in Australia where more pingueculae were found than pterygia. [39] The Australia survey involved individuals aged 49 years and older which possibly explains the difference found. Furthermore our study was hospital based and therefore it involved those who had symptoms and came to seek medical attention. In view of this more subjects with pterygia than pingueculae were obtained in our study as they presented due to visual symptoms or cosmetic problems associated with pterygia. Pinguecula rarely cause problems unless they are inflamed or have increased in size.

Six growths in this study showed mixed features. Histological features of pterygium were also found in three squamous cell carcinomas, two dysplasias and a compound naevus. It is possible that there was malignant transformation from pterygium to dysplasia and squamous cell carcinoma. Similarly in Italy a case of an apparently trivial pterygium was found to be a conjunctival intraepithelial neoplasia after

histological study. [47] This justifies the importance of histological study of conjunctival growths.

One growth was a granuloma pyogenicum. This growth was from an 8 years old boy who also had allergic conjunctivitis. There was no history of trauma or surgery. Pyogenic granulomas are said to develop in areas of previous trauma or inflammation. It is therefore possible that in this boy it arose following inflammation due to allergic conjunctivitis.

Presence of calcification in the growth

Our study showed that clinical calcification was present in almost half of the squamous cell carcinomas, carcinoma is situ and dysplasias (Table 11). The two squamous cell carcinomas and dysplastic growths, which showed features of pterygium, were also calcified clinically. Few pterygia and pingueculae showed calcification. However microscopically calcification was evident in only one pterygium. We can therefore conclude that calcification is not related to malignant transformation. Calcification is a rare phenomenon in the conjunctiva. [23] When present it is usually dystrophic in nature (occurring in areas of cell injury or necrosis). [23]

Association between histological pattern and HIV infection

The emergence of the HIV/AIDS pandemic has caused a significant change in the epidemiological picture of conjunctival tumours. This is evidenced by a number of studies done in different parts of the world including sub-Saharan Africa.[3,4,17,18,19,20,93]

Squamous cell carcinoma, Kaposis's sarcoma and B-cell non Hodgkin's lymphoma have been reported to be highly associated with HIV infection. [3, 4, 6, 16, 17, 18, 19, 20]

In our study 42.5% of subjects were HIV seropositive, majority being females (Table 12). This finding is within the range (<3% to >44.4%) reported for this country. [22] Several reasons can be advanced to explain this high percentage. This study involved an urban population, which is expected to have high prevalence of HIV infection. [22]

The female predominance was not statistically significant as this was due to the predominance of females in the study population. The proportion of HIV seropositive females and males was almost equal (Table 12).

Forty-seven (92.1%) of HIV positive patients in this study were in the age group of 16-45 years. This age group includes sexually active members of the community and are therefore highly at risk of acquiring HIV infection. [22]

Malignant conjunctival growths (squamous cell carcinoma and Kaposi's sarcoma) were found to be significantly associated with HIV infection (P value<0.01). These finding agree with those obtained In Uganda, Malawi and USA. [3, 18, 93] Together with squamous cell carcinoma and Kaposi's sarcoma, B-cell non-Hodgkin's lymphoma has also been reported to be associated with HIV infection. [18]

However none of the conjunctival growths in this study showed histological features of a lymphoma.

Conjunctival squamous cell carcinoma and HIV infection

In this study 74.4% of patients who had squamous cell carcinoma were HIV seropositive. This finding agrees with that obtained in Uganda. [3] The majority (89.7%) of these patients were in the age group of 16-45 years. A study done in Congo showed the age group to be 25-46 years. [5] Conjunctival squamous cell carcinoma in HIV infected individuals is noted to occur in a younger age group compared to the immunocompetent individuals. [5, 6] This early presentation of squamous cell carcinoma in HIV infection is explained by the immunosuppressive effect of the virus, which enhances the development of squamous cell carcinoma precancerous lesions. [92]

The immunosuppressive effect of HIV is also said to promote the development of HPV related precancerous lesions. [92] One study showed presence of HPV-16 in 35% of HIV infected patients with invasive squamous cell carcinoma of the conjunctiva. [93] It is also reported that generally HPV associated malignancies occur at increased rates in individuals with HIV/AIDS. [96]

Eighty percent of HIV negative patients with squamous cell carcinoma in this study were in the age group of 16 –45 years. This shows that regardless of HIV infection, other factors may influence the early presentation of conjunctival squamous cell carcinoma. Exposure to ultraviolet B rays has been reported to be associated with an increased incidence and early presentation of this tumour. [6] An almost 50% increase in incidence of conjunctival squamous cell carcinoma for every 10 degrees decrease

in latitude has been reported. [95] This disease is therefore said to represent a model of multifactorial epithelial carcinogenesis.

Conjunctival Kaposi's sarcoma and HIV infection.

In this study, 91.7% of patients with Kaposi's sarcoma were HIV seropositive. This figure agrees with that obtained in Zaire. [97] In 9 patients KS was involving the conjunctiva only with bilateral involvement noted in two cases. Three patients showed skin involvement (eyelids chest and upper limbs). This shows that conjunctival involvement may be the first and initially the only clinical manifestation of KS in HIV infected patients.

One patient was found to have conjunctival candidiasis. This patient was also HIV seropositive. We can note that opportunistic fungal infection may present as a conjunctival growth in HIV positive patients.

CONCLUSIONS AND RECOMMENDATIOS

This study has shown that Tanzania is experiencing an epidemic of conjuntival squamous cell carcinoma and Kaposi's sarcoma similar to that seen in other African countries. The tumours occur in patients of relatively young age. The epidemic is significantly associated with HIV infection.

The commonest benign conjunctival growth in this study was pterygium.

We have also noted that malignant change may occur in a clinically benign growth.

In the light of this study it is recommended that: -

1.Early surgical excision of suspicious conjunctival growths for histological study so as to rule out malignancy and hence prevent delay in treatment.

2.There is need to evaluate the association between the degree of immunodeficiency caused by HIV infection and development of conjunctival tumours. Evaluating the CD4+ T Cell count in HIV seropositive patients with conjunctival tumours is recommended in order to establish a temporal relationship between HIV infection and development of conjunctival tumours for academic purposes.

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