

Eye Pathology Update

Update on Pathologic Diagnosis of Corneal Infections and Inflammations

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ABSTRACT

One of the most frequent types of corneal specimen that we received in our pathology laboratory is an excised corneal tissue following keratoplasty. Several of these cases are due to corneal infections or the sequelae, like corneal scar. Advances in the histological and molecular diagnosis of corneal infections and inflammations have resulted in rapid and accurate diagnosis of the infectious agent and in the overall understanding of the mechanisms in inflammatory diseases of the cornea. This review provides an update of histopathological findings in various corneal infections and inflammations.

Key words: Corneal Histopathology, Corneal Infiltrate, Corneal Inflammations, Microbial Keratitis, Moorens' Ulcer

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INTRODUCTION

Keratitis is an important cause of ocular morbidity worldwide, the outcome of which depends on early diagnosis, prompt and effective treatment and various host and agent factors.¹ Some of the common causes of infectious keratitis include bacterial, fungal, viral, and protozoan, the diagnosis of which is made on clinical examination aided by microbiological demonstration in smears or cultures from corneal tissues. Non-infectious keratitis can also be seen in several conditions where inflammation occurs in the cornea due to other etiologies, leading to corneal vascularization, scarring and visual loss. This chapter provides an update on corneal infections and inflammations with emphasis on the histopathological features.

SECTION 1: CORNEAL INFECTIONS

Histopathology of corneal infections-general considerations

Corneal tissues require edge embedding to retain proper orientation of corneal layers. Histological features of keratitis reflect the features seen on slit lamp examination or by confocal examination of the eye.

Corneal infections often commence as epithelial ulceration followed by stromal infiltration by polymorphonuclear (PMN) and lymphomononuclear cells leading to destruction of Bowman's layer, stromal necrosis and perforation of the Descemet's membrane in severe cases. Suppurative infections like bacterial and fungal lead to infiltrates in anterior 2/3 of stroma and abscess formation. Chronic infections show epithelial regeneration, vascularization, edema, giant cell reaction, myofibroblastic transformation and stromal remodeling (scarring) and round cell infiltration. Table 1 provides a guideline on evaluation of corneal layers in infectious keratitis. In addition to routine hematoxylin and eosin (H and E) and periodic acid Schiff stain (PAS); appropriate special stains are useful in identifying the organisms.

HISTOPATHOLOGY OF SPECIFIC INFECTIONS

Bacterial keratitis- histopathology

Bacterial infections result in epithelial ulceration, with destruction of Bowman's layer and anterior stroma with severe and diffuse infiltration PMNs. The stromal thinning, destruction

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Table 1: Summary of histological features in infection in cornea

Anatomic layer	Histologic features to be observed	Remarks
General features	Thickness, thinning, necrosis, perforation, separation, exudates, pigmentation	
Epithelium	Intactness, edema, ulceration, hyperplasia, down growths inflammatory infiltrates, giant cell reaction, cytoplasmic inclusions regularity/breaks of basement membrane, pannus formation (inflammatory or degenerative)	Periodic acid Schiff (PAS) stain is complementary to hematoxylin and eosin
Bowman's layer	Thickness, breaks, absence, calcification, degenerative changes, any deposits	Special stains as and when required
Stroma	Thinning, edema, vascularization, inflammation and density and type of inflammatory cells (neutrophils, lymphocytes, plasma cells, giant cells, location of cells (anterior/ mid/posterior stroma), perforation, cellularity, changes in keratocytes (myofibroblastic transformation, loss of keratocytes) orientation of collagen fibers, fibrosis, scarring, abnormal deposits, any infectious agent and its load and location	Special stains as and when required for fungus, bacteria, acanthamoeba and microsporidia
Descemet's membrane (DM) and endothelium	Thin, fragmented or intact. Giant cell reaction around DM, granulomatous inflammation around fragmented ends Presence of microorganisms (like fungus), presence and adequacy of endothelial cells, morphology of endothelial cells, retrocorneal membrane and exudates adherent to DM, anterior chamber exudates	PAS stain, Gomori methenamine stain (GMS)
Others	Adherent uveal tissue, AC exudates	

is contributed by collagenolytic enzymes released by the PMNs and bacterial endotoxins which leave behind nuclear debris. If left unattended, it results in perforation with herniation of iris into the site forming a pseudocornea. Use of cyanoacrylate glue could be seen in the form of refractile wavy unstained glue on the surface with scalloping margins, appreciated better with lowered condenser. Bacteria on histologic sections are appreciated when present in colonies and with the use of Grams stain. Etiologic agents include Gram-positive bacteria are *Staphylococcus* and *Streptococcus* sp, *Neisseria gonorrhoea* and *Pseudomonas* species which can penetrate intact epithelium and other *Enterobacteriaceae* are the primary Gram-negative pathogens involved in microbial keratitis. Gram-negative infection show relatively a rapid pace of inflammation, often leading to severe corneal abscess and perforation with hypopyon. Unusual patterns of bacterial keratitis can be seen in infectious crystalline keratitis, commonly seen in corneal grafts or with the use of steroids. Bacterial colonies develop a biofilm thus appearing as discrete and viable colonies with fine, needle like extensions within the corneal stroma, (resembling crystals) with minimal

stromal inflammation. The most common organism implicated is alpha-hemolytic streptococci.¹

Pathology of Keratitis

This accounts for up to 44% of central corneal ulcers in South India.²

Histopathology

Corneal epithelium is usually ulcerated, accompanied by edema, severe inflammation and stromal thinning. Density and extent of inflammation and necrosis depends on the mode of injury, duration of insult, treatment received and the local and systemic condition of the host. In our series, we observed that in the early stages the inflammation is focal, patchy and mostly involves the anterior two thirds of the stroma; with satellite lesions or abscesses in the surrounding stroma. The posterior stroma when affected may show loss of stromal keratocytes due to apoptosis. Later these abscesses become confluent, extend to deep stroma, and lead to total destruction of stromal architecture with necrosis and perforation. Predominantly deep seated lesions along with anterior chamber exudates and hypopyon, with relative sparing of superficial stroma are noted in a few cases. Some of the cases could represent fungal keratitis superadded to a pre-existing viral infection. Granulomatous inflammation or giant cell reaction has been reported as 14 % of cases.² Fungus on routine stains appears as hollow, unstained filaments with two parallel borders. Identification is easier with special stains (PAS, Gomori methenamine silver stain (GMS)) which highlight the hyphate filaments, measuring up to 10 μ in diameter, and of varying lengths. The filaments can be broken, or cross section or end-on, through all the layers including within the Descemet's membrane (DM) [Figure 1a and 1b].

Although histopathology with special stains has a high yield in the detection of fungus, it may be negative in one-third of cases, especially in late stages of disease. This may be either simply because of sampling error or due to elimination of the fungus by prior medical therapy.² We also observed an interesting association between inflammatory cells and fungus distribution. Fewer filaments are seen in the region of dense inflammation whereas high concentration is noted more commonly beyond the zone of inflammation, into the posterior stroma, suggesting that fungus would penetrate beyond the clinically evident zone of infiltration. Other changes found in fungal keratitis are granulomatous inflammation, especially in the posterior stroma, vascularization in advanced disease and satellite lesions. An interesting variant of fungal infection is dematiaceous fungal keratitis, which presents like a dry raised pigmented plaque on the surface of cornea.³ The excised plaque shows a carpet-like growth of filaments on the surface with variable pigmentation which can be identified even in H and E, with minimal inflammation and necrosis.

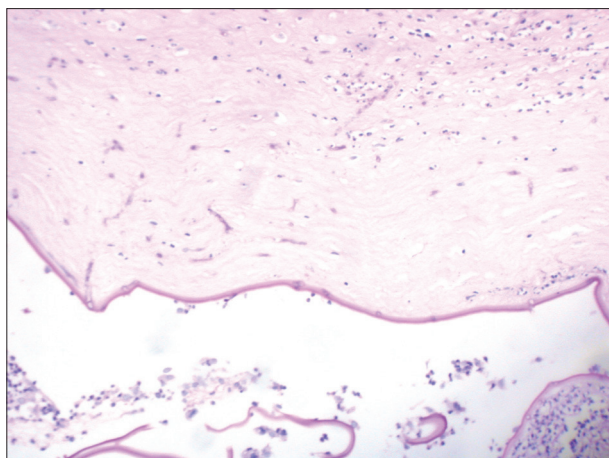


Figure 1a: Section of posterior cornea showing stromal edema and fragmented Descemet's membrane (DM) in a case of perforated fungal corneal ulcer. Fungal filaments are easily identified in the posterior stroma, noted in the DM also. Note the relative sparse distribution of inflammatory cells in the deeper stroma (H and E, ×400)

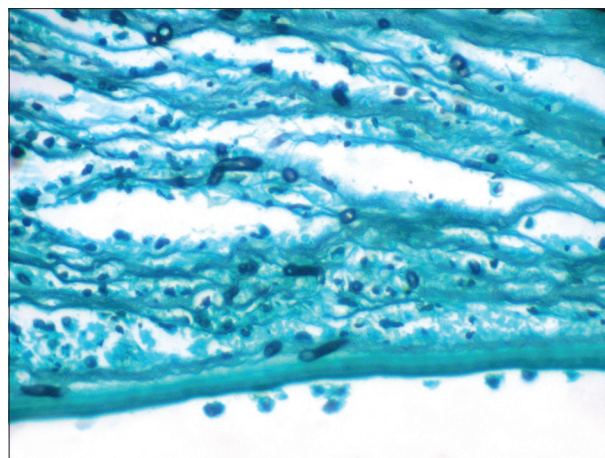


Figure 1b: On special stains, the fungal filaments are easily seen as silver-impregnated septate, hyaline, filaments (modified Gomori methenamine silver preparation, ×400)

Viral keratitis

Herpes simplex virus (HSV) serotypes 1, 2 commonly affect the cornea. Involvement ranges from epithelial disease (dendritic ulcer) to stromal keratitis, endotheliitis, keratouveitis and metaherpetic keratitis.⁴ Primary forms of stromal disease from HSV include necrotizing stromal keratitis (NSK) and immune stromal keratitis (ISK).

Necrotising stromal keratitis

Direct invasion and replicating virus and severe host inflammatory response leads to destructive stromal inflammation that is often refractory to treatment. Single or multiple, gray-white, creamy homogenous abscesses with edema, secondary guttate, severe iridocyclitis, hypopyon and secondary glaucoma are noted.

Histopathology of necrotizing stromal keratitis

Corneal epithelium may be intact or ulcerated. Neutrophilic stromal infiltrates can be focal, diffuse or stratified or coalescent abscesses; depending upon severity of inflammation.

Epithelial regeneration, round cell infiltrates with multinucleate giant cells (MNG) with or without inclusion bodies, could be around the DM, is indicative but not diagnostic of HSV. Stromal edema and DM folds are noted. In extreme cases, intense stromal loss and necrosis can lead to descemetocoele or perforation. Vascularization is a prominent feature, seen at any level, progressing toward the site of active inflammation. In NSK, HSV antigen has been documented in epithelial cells and to some extent in keratocytes, endothelial cells, and in MNG cells around DM. Electron microscopy can detect intact viruses.⁵

Immune stromal keratitis

ISK may be a continuum of NSK and is a chronic recurrent manifestation, occurring in 20% of population with ocular. It is predominantly immune mediated although direct invasion and

active replication of virus may play a role.⁵ The mechanism of inflammation is thought to be due to retained viral antigen within the stroma that triggers antigen antibody complement cascade (AAC) that results in intrastromal inflammation. Evidence also suggests that HSV-1 disrupts the normal equilibrium between angiogenic and anti-angiogenic stimuli leading to vascularization.

Histopathology of immune stromal keratitis

Since this entity is more due to the persistence of inflammation, epithelium is usually intact with minimal inflammation. Stromal mixed inflammatory infiltrates of varying degree could be focal, multifocal or diffuse, associated with stromal edema. Rapid neovascularization with multiple fronds of new vessels or ghost vessels with perivascular cuffing is a common feature. Other changes suggestive of its chronicity are ingrowth of pannus, fragmented Bowman's layer, lipid keratopathy, stromal scarring, granulomatous reaction around DM, duplication of DM and retro-corneal membrane [Figure 2a and 2b].

Acanthamoeba keratitis

Histopathology

In addition to epithelial ulceration, destruction of Bowman's layer, and stromal inflammation, there is presence of cysts and trophozoites of *Acanthamoeba* apoptosis of keratocytes.⁶ Cysts are seen as oval, double-walled structures with paracentral nucleus, the wall stain prominently with H and E or PAS and GMS [Figure 3a and 3b]. Trophozoites are noted within the collagen lamellae as elongated structures, larger than keratocytic nuclei. Unusual features like granulomatous inflammation, vascularization and loss of keratocytes in deeper stroma which are postulated to be due to apoptosis of stromal keratocytes have also been reported.⁷

Nocardia keratitis

Nocardia are filamentous beaded bacilli, belonging to the order

actinomycetales. It is a rare cause of infectious keratitis⁸ and the following species have been reported more often: *Nocardia asteroides* (commonest), *N. gypsoidea*, *N. brasiliensis*, *N. caviae* and *N. farcinic*. Factors predisposing to infection include trauma with soil, use of corticosteroids, surgery and contact lens wear.⁹

Histopathology

Since this infection is seen in unusual settings, the corneal specimen could be a corneal biopsy, amputated flap LASIK; or corneal button following either lamellar or penetrating keratoplasty. There is often epithelial ulceration with severe stromal loss and intense inflammatory infiltrates. The bacilli itself can be seen as clusters of Gram-positive filaments (with branching) noted within the necrotic areas in post-LASIK⁹ and post-PRK¹⁰ infections; appearing bright red on acid fast staining with 1% modified Ziehl–Neelson stain as bright red filaments seen at 1000 x magnification (oil immersion). These organisms can also be noted at the edge of the inflammatory foci. In cases pre-treated with corticosteroids, clusters of *Nocardia* appearing as colonies can also be noted. Generally the organisms appear limited to anterior and mid-stroma on histopathology and do not appear to breach the DM.

Atypical mycobacterial keratitis

Histopathology

In most cases, epithelial ulceration, stromal necrosis and tissue loss and dense infiltration by acute and chronic inflammatory is seen. Development of granulomatous inflammation has been described and appears to play a role in preventing the spread and in clearing the bacteria from the infected tissue. In cases where corticosteroids have been used, there is suppression of granulomatous inflammation and this may account for the severe and prolonged keratitis seen clinically.¹¹ On histological examination, cases pre-treated with steroids would show stromal thinning and paucity of inflammatory cells. The organisms may be noted as dense colonies within the corneal stromal pockets, or in amputated LASIK flaps.¹²

Microsporidial keratitis

Microsporidia are spore forming parasites and is an emerging cause of keratitis.¹³ There are two clinical presentations of ocular microsporidial infections: corneal stromal keratitis and epithelial keratopathy with conjunctivitis.

Histopathology

The cornea may show varying degrees of inflammation based on whether corticosteroids were used. The microsporidial spores are faintly stained and can be easily overlooked by inexperienced pathologists in routine H and E stains. They appear oval to round, brown in color and the internal band girding the spore appearing like a “waist band” [Figure 4a and 4b]. Though many stains highlight the spores like 1% acid fast stain, GMS, calcofluor white (CFW) with potassium hydroxide (KOH),

Masson’s trichrome, [Figure 3], we find 1% acid fast stain easy, economical with good inter-observer agreement.¹⁴

Miscellaneous infections

Treponema pallidum

This causes Syphilitic stromal (interstitial) keratitis. Congenital syphilis can present with stromal inflammation between the ages of 5 and 15. Histological study has been possible in only a few cases and shows a thickened cornea, diffuse and localized lymphocytic infiltration in middle and posterior stroma and vascularization. In chronic keratitis, healed lesions would be noted as fibrous pannus, ghost vessels, stromal scarring, and DM thickening. *Treponema pallidum* organisms have not been isolated from these lesions.¹⁵

Mycobacterium tuberculosis

Patients with systemic tuberculosis have chronic corneal inflammation and lesions near the limbus called phlyctenules. Histologically, this consists of anterior to midstromal focus of sub-acute and chronic inflammatory cells with necrosis of collagen, and replacement by vessels and scar tissue in chronic stage. Tubercle bacilli have not been identified in these lesions and it appears to be a hypersensitivity reaction.¹⁵

Mycobacterium leprae

Corneal disease is frequently seen in long-standing leprosy, either directly as an infection due to lepra bacilli or secondary to chronic ocular changes like exposure keratopathy. Histological, lepromatous leprosy produces a non-ulcerating diffuse granulomatous stromal infiltration characterized by infiltration with foamy histiocytes and giant cells. These cells contain lepra bacilli, picked up on acid fast staining.¹⁵

Onchocerciasis

Infection by *Onchocerciasis volvulus* is one of the leading causes of blindness worldwide. Microfilaria has been observed in all ocular tissues and migrates easily to the cornea. Histologically intact microfilaria with scant inflammation is noted. In case of degenerated organisms, intense eosinophilic response is noted with secondary changes in all layers of cornea, like epithelial edema, bullae, replacement of Bowman’s layer by inflammatory pannus and stromal vascularization and fibrosis.¹⁵

SECTION 2: INFLAMMATIONS

Inflammation of the cornea differs in many respects from that of other body sites due to its avascularity. In the following section, the pathological changes in non-infectious corneal inflammatory diseases which include idiopathic diseases like peripheral ulcerative keratitis, Mooren’s ulcer, Terrien’s marginal degeneration and specific corneal inflammation like graft rejection, corneal melt and bullous keratopathy and will be elaborated upon.

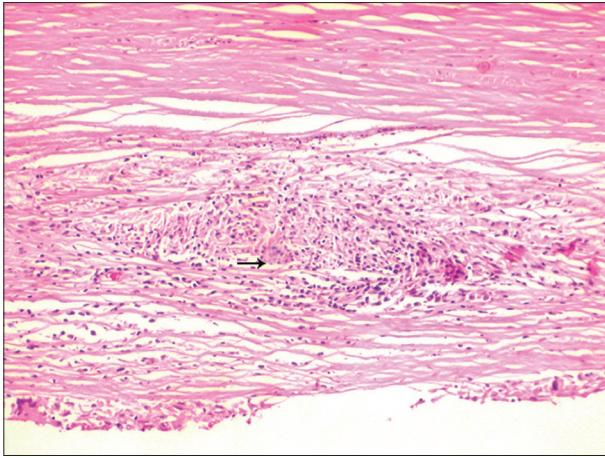


Figure 2a: Section of the cornea showing patchy inflammation consisting of mixed inflammatory cells. Note the presence of granulomas and giant cells (arrow) in the deep stroma, highly suggestive of viral keratitis (H and E, $\times 400$)

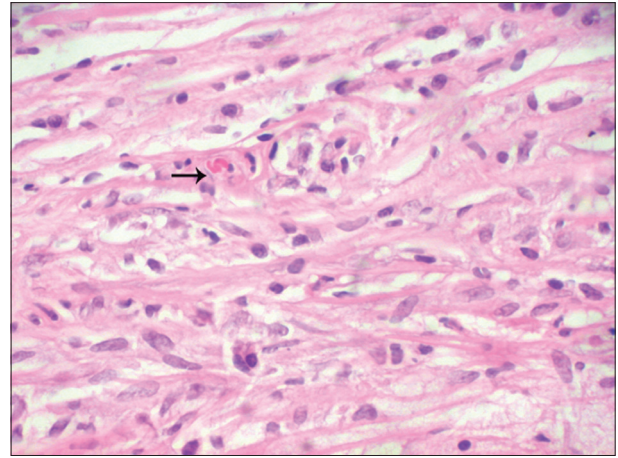


Figure 2b: At high magnification, prominent fibroblastic nuclei and blood vessels (arrow) are noted (H and E, $\times 1000$)

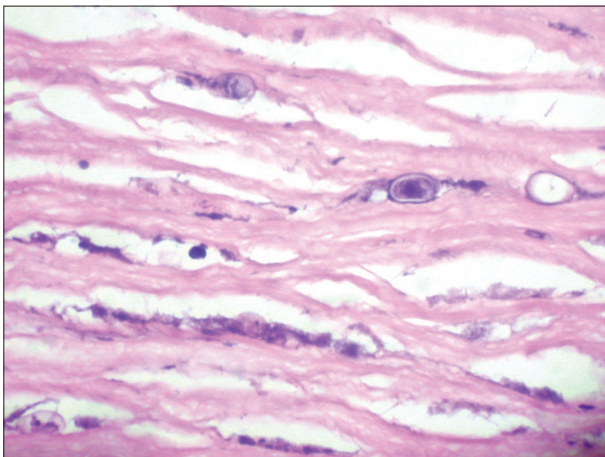


Figure 3a: Microphotograph showing corneal stroma with acanthamoeba cysts noted as prominent double walled structures of intact cysts as well as presence of degenerating cysts (H and E, $\times 1000$)



Figure 3b: On special stains, the intact and degenerating cysts (arrow) are easily identified (Modified Gomori methenamine silver preparation, $\times 1000$)

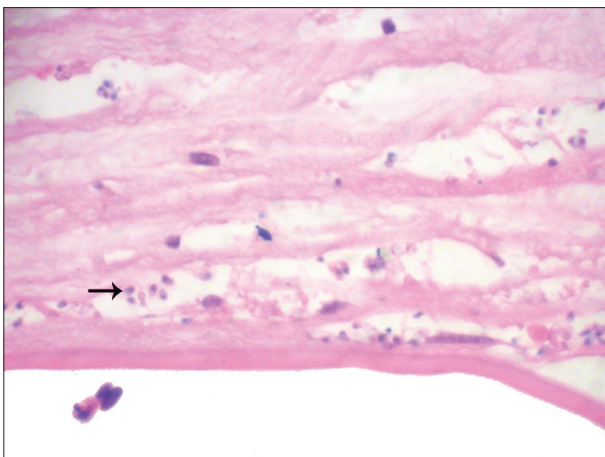


Figure 4a: Section of posterior stroma showing tiny microsporidial spores (arrow) located within the lamellar spaces (H and E, $\times 1000$)

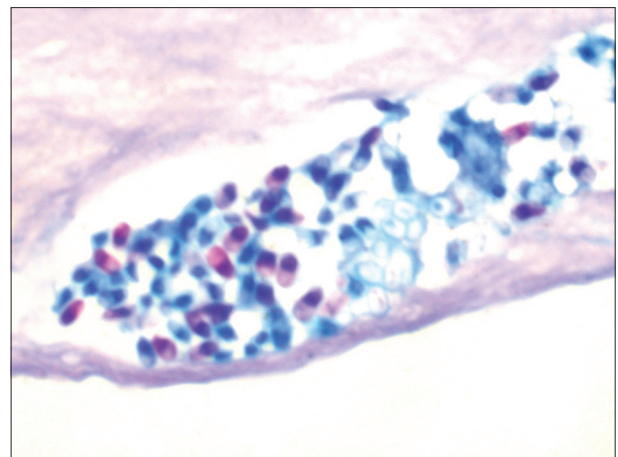


Figure 4b: On 1% acid fast stain, the spores are seen as pink-staining structures with prominent nucleus and characteristic waist-band (1% acid fast stain, $\times 1000$)

Idiopathic keratitis

Peripheral ulcerative keratitis

Noninfectious/inflammatory keratitis can be subdivided into micro-ulcerative and macro-ulcerative. Micro-ulcerative peripheral keratitis includes marginal catarrhal ulcer, phlyctenulosis and peripheral rosacea keratitis. Macro-ulcerative peripheral keratitis is generally a manifestation of systemic, immune-mediated disease. PUK has been associated with nearly all connective tissue diseases or vasculitides. However, the most common entities associated with are rheumatoid arthritis, Wegener's granulomatosis and polyarteritis nodosa.

Histopathology

Catarrhal ulcers are due to type III immune response in which antigens that have diffused into the cornea react with antibodies from the limbal blood vessel, and the resulting antigen-antibody complexes incite a local polymorphonuclear inflammatory response. Phlyctenules are a type IV, or delayed hypersensitivity response, pathologically characterized by infiltration of lymphocytes, plasma cells and macrophages in addition to polymorphonuclear leucocytes.

When associated with systemic disease, PUK represents a local vasculitis affecting the limbal arcades. Circulating immune complexes deposit in the limbal vessels inciting local inflammation, which include diffusion of immune complexes, components of complement system, and inflammatory cells into the peripheral cornea.¹⁶ Loss of stromal collagen leading to descemetocele formation has been reported.

Mooren's Ulcer

It is an inflammatory disorder of presumed autoimmune etiology characterized by progressive circumferential peripheral, stromal ulceration with a variable clinical course. It affects males more often and is bilateral in about 25% of patients. Symptoms include severe pain, photophobia and blurred vision due to astigmatism. Typically it begins as a crescent-shaped gray white infiltrate in the peripheral cornea. This is followed by epithelial breakdown and stromal melting. Progressive circumferential and central stromal thinning is associated with an undermined and infiltrated leading edge. The healing stage is characterized by thinning, scarring and vascularization.

Histopathology

Though the etiopathogenesis of Mooren's ulcer is unknown, accumulating evidence suggested it to be a localized autoimmune disorder. The initial evidence was pathologic. Resected conjunctiva from patients with Mooren's ulcer showed large number of plasma cells, lymphocytes and histiocytes. The conjunctiva adjacent to the ulcer area shows increased collagenolytic enzyme. Circulating antibodies to human corneal epithelium were seen in the serum of patients with Mooren's ulcer. Evidence that both cellular and humoral autoimmune phenomenon play a

major role in the pathogenesis of disease includes findings on histopathological examination: a predominance of active plasma cells, polymorphonuclear leucocytes, eosinophils, mast cells, immunoglobulins. In some patients, suppressor/cytotoxic T cells are reduced as in many autoimmune disease processes.

Histopathologically, non-specific necrosis of the epithelium and Bowman's layer with cell debris within the base of the ulcer is noticed. Infiltration of plasma cell and lymphocytes are minimal. Gross disorganization of anterior stromal lamellae with dissolution of collagen fibrils and ground substance into filamentous and granular materials in association with polymorphonuclear leucocytes were observed in electron microscopic examination.¹⁷

The posterior lamellae, Descemet's membrane and endothelium remain intact. Aronson and coauthors noted the discrepancy between the excessive tissue necrosis and the minimal inflammatory reaction in this disease.¹⁸

Terrien's marginal degeneration

It is an uncommon peripheral inflammatory condition though often included in degenerative condition. It is often bilateral and affects age group between 20 and 40 years. Males are more affected than females (3:1).¹⁹ The lesion usually begins superonasally with fine punctate opacities in the anterior stroma frequently associated with mild superficial vascularization. It gradually spreads circumferentially with a lucent area to the limbus. Progressive circumferential thinning results in a peripheral gutter. A yellow-white zone of lipid can be seen central to the advancing zone of the gutter. Gradual vision deterioration occurs as a result of increasing astigmatism. Two types of Terrien's disease have been described. While the more common quiescent type occurs in older patients, inflammatory Terrien's degeneration occurs in younger individuals. These patients have recurrent episode of disabling pain and inflammation, episcleritis and scleritis.²⁰

Histopathology

The epithelium may be normal, thick, or thinned. Bowman's layer is fragmented or absent. Fibrillar degeneration of collagen is seen in histopathological examination. Break in Descemet's may be seen. Fibrous tissue can be seen repairing Descemet's membrane. Lipid deposition consists of cholesterol crystal. Inflammatory cells are sparse without any definite infiltrate. Centrally there is an abrupt demarcation between degenerated stroma and the adjacent normal parenchyma. Binder *et al.*, have reported lymphocyte and plasma cell infiltrate and suggested a relationship between Terrien's degeneration and Mooren's ulcer.²¹ Lopez *et al.*, have demonstrated a difference in the proportion of B cells in both the disease suggesting the difference in the activity and pathogenesis of the disease.²²

Miscellaneous causes

Graft Rejection

Histopathology

Corneal transplant rejection is caused by an active immunological reaction against histocompatibility antigens of the donor tissue. Most histopathological studies of the corneal transplants immune reactions in humans have been carried out in late stages. Endothelium is usually absent in such cases. The early reaction after immune rejection has been investigated in experimental animals.

Epithelial rejection is due to proliferation of lymphocytes and plasma cells from vessels at the wound margin and from superficial stroma. The immune reaction in the stroma is manifested as an infiltration of lymphocytes and in later stages, of capillaries and fibroblasts. The endothelial rejection occurs as a progressive process with formation of the “Khodadoust line” which is a collection of lymphocytes. It may be associated with deep vascularization of the stroma.

Corneal Melt Secondary following the use of non-steroidal anti-inflammatory agents

Histopathology

Topical non-steroidal anti-inflammatory drugs have been reported to be the cause of corneal melting and perforation.²³ Impairment of wound healing, neurotrophic effect and activation of matrix metalloproteinase are responsible for the melting.²⁴ Gokhale *et al.*, have reported a case of diclofenac-induced acute corneal melt after collagen cross linking.²⁵ The surrounding cornea of perforation showed regenerative changes with large epithelial cells. The adjacent stroma showed edema, keratocyte loss, myofibroblastic transformation of keratocytes, and few neutrophils and round cell infiltrate. The presence of neutrophil and mononuclear leucocytes were also reported from earlier studies.

Bullous keratopathy

Clinically characterized by recurrent episodes of pain, redness and foreign body sensation due to rupture of the corneal bullae, it is primary not an inflammatory condition but a non-specific sequelae to the long standing stromal and epithelial edema caused by endothelial decompensation due to any cause. The epithelium is separated from the underlying Bowman's layer by an influx of fluid. Thickening and reduplication of the underlying basement membrane is commonly seen. Ingrowths of collagen may be seen between the epithelium and Bowman's layer in some cases. Although, it is difficult to diagnose early stromal edema in advanced stage, one can recognize increased thickness of cornea and more obvious clefts in between lamellae. One can find infiltrates of leucocytes between the collagen fibers in later stages. The endothelial cells show marked vacuolization and may be extremely thin or absent. Descemet's membrane usually show thickening.

CONCLUSION

In summary, histological diagnosis of corneal infections contributes to clinical management especially when a prior etiologic diagnosis is not available. In case of corneal infections, histology helps establish the etiologic diagnosis based on the type of inflammatory response and also the identification of the specific organisms within the excised tissue. However, in the diagnosis of corneal inflammation, most of the times it is non-specific and requires clinical correlation and the exclusion of various infective causes.

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Author Help: Reference checking facility

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- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. *Otolaryngol Head Neck Surg* 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.