

### **The Eye at Autopsy**

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#### **Take-Home Points:**

- A complete autopsy should include the eyes, similar to any other major organ of the body
- 30% of autopsies have major postmortem ophthalmic findings, i.e., those likely to have required patient management and/or may have important medical implications for close relatives
- 60% of autopsies have minor postmortem ophthalmic findings (those that may have eventually required treatment or occurring after eye surgery)
- Examination of autopsy eyes is essential for pathology and ophthalmology residents to understand normal ocular anatomy and the changes that result from aging
- Autopsy eyes are a critical resource for advancing our knowledge of human disease

#### **Why perform an autopsy?**

- 1) Autopsy: Aiding the Living by Understanding Death, College of American Pathologists, 2001
  - Primary purpose: To answer any questions the family or physician may have about the illness, cause of death, and/or any co-existing conditions
  - Establishing cause of death may be source of comfort for family
  - Determine if there are heritable problems
  - What is learned through an autopsy may help save lives of others with similar conditions
- 2) Stated goals of Duke autopsy service (resident review committee)
  - To provide feedback to physicians and family regarding the disease processes at the time of a patient's death
  - To provide training in the principles and practice of anatomic pathology through the performance of autopsies
- 3) A complete autopsy, including examination of the eyes, is necessary "to answer any questions the family or physician may have about the illness, cause of death, and/or any co-existing conditions"

#### **Duke University Health System Autopsy Permit**

"I hereby authorize Duke University Medical Center, and such persons as it may designate, to perform a complete postmortem examination on the remains of \_\_\_\_\_. I authorize the examining physician to remove such specimens, tissues and/or organs, and to retain, preserve and/or contribute the same for such diagnostic, therapeutic or other scientific purposes as may be deemed proper. An unrestricted autopsy may examination of heart, brain, lungs, eyes, kidneys and any other organ or tissue deemed necessary. The examination and tests

may include, among others, tests for infectious diseases such as tuberculosis (TB), hepatitis, syphilis, cytomegalovirus, human immunodeficiency virus (HIV or AIDS), etc. The results of all tests will become part of the patient's medical records and may be reported to health authorities when appropriate. This authorization is limited by the following expressed conditions; (List limitations, if any) \_\_\_\_\_.”

#### **Duke University Hospital Decedent Care Service**

- 1) Staffed 24 hours per day, 7 days per week
- 2) Meet with next-of-kin after all deaths
- 3) Coordinate details surrounding death, i.e., transportation of bodies, funeral home arrangements, and whether or not an autopsy is desired
- 4) Read autopsy permit to next-of-kin, complete form, and document details of the meeting with the next-of-kin

#### **K.J. Butnor and A.D. Proia, Unexpected autopsy findings arising from postmortem ocular examination, *Arch Pathol Lab Med* 2001;125:1193-1196.**

- 1) Review of 277 consecutive autopsies in which eyes were removed for examination
- 2) 20% of all autopsies had eyes examined
- 3) Major postmortem ophthalmic findings
  - a. Major: Contributed to death; were likely to have required patient management; and/or may have important medical implications for close relatives
    - i. Diabetic retinopathy 39 cases (14%)
    - ii. Age-related macular degeneration 14 cases (5%)
    - iii. Optic nerve atrophy 12 cases (4%)
    - iv. Glaucoma, chronic 5 cases (2%)
- 4) Minor postmortem ophthalmic findings
  - a. Minor: May have eventually required treatment; findings that would be reasonably expected after ocular surgery
    - i. Chronic uveitis 77 cases (28%)
    - ii. S/P extracapsular extraction/intraocular lens implant 43 cases (16%)
    - iii. Soemmerring ring cataract 40 cases (14%)
    - iv. Cataract 20 cases (7%)
    - v. Diabetes-associated ciliary body thickening 18 cases (6%)

#### **Medical Assistant on the World Wide Web (MAW<sup>3</sup>)**

- 1) Electronic autopsy report system introduced in September 2000 (MAW<sup>3</sup>)
  - a. Reports are fully searchable
  - b. Internet accessible
  - c. Patient data secure
- 2) Autopsy diagnoses from 1994 – August 2000 added in MAW<sup>3</sup>
  - a. 3077 adult patients
  - b. 501 pediatric patients
  - c. 332 Stillborn infants

- 3) Autopsy cases and eyes examined 2005-2007
  - a. 2005: 272 autopsies, 113 sets of eyes (42%)
  - b. 2006: 326 autopsies, 134 sets of eyes (41%)
  - c. 2007: 341 autopsies, 149 sets of eyes (44%)
- 4) MAW<sup>3</sup> search on 01/27/08: 1025 autopsies with eye examination
  - a. 162 autopsies with “choroiditis”
  - b. 99 autopsies with diabetic retinopathy
  - c. 71 autopsies with “age-related macular degeneration”
  - d. 48 autopsies with “glaucoma”
  - e. 19 autopsies with serous detachment of retina and/or RPE
  - f. 13 autopsies from men on Flomax
  - g. 5 sets of eyes from patients with SLE
  - h. 3 sets of eyes from patients with ALS
  - i. 2 autopsies with polymorphic amyloid degeneration

**Case studies of autopsy eye findings to illustrate the value of postmortem eye examination**

- 1) Age-related macular degeneration
- 2) Non-proliferative and proliferative diabetic retinopathy
- 3) Open-angle glaucoma
- 4) Serous detachment of the RPE in systemic lupus erythematosus
- 5) Sickle cell retinopathy
- 6) Polymorphic amyloid degeneration

**Conclusion**

Examination of eyes at autopsy is essential for a complete autopsy report, as well as providing an important resource for teaching and research.

## 2008 Ophthalmic Pathology Companion Meeting USCAP

What does 'blind, painful' eye really mean?

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**The answers to the question “what does ‘blind, painful’ eye mean” depend on the persons to whom it is posed. To the patient, it is literal: the eye is functionally or virtually non-seeing and causes one unremitting discomfort or pain not remedied by other means. To the ophthalmologist, it is a reason for enucleation in that it is a ‘cure’ for the patient’s symptoms. Unfortunately, it is also a convenient catch-all phrase for the requisition sheet to the pathologist. To the pathologist, it is meaningless, in that it provides no useful information about the etiology or etiologies resulting in such a condition. To the surgeon’s defense, enucleation is often performed by an oculoplastic surgeon, not the patient’s primary ophthalmologist or specialist, and the oculoplastic surgeon may have no more information about the patient’s history to provide. Thus, attempts by the pathologist to track down clinical history may be time-consuming, difficult and ultimately fruitless. So what may we pathologists glean from examination of the ‘blind, painful’ eye? What is important for the patient and the ophthalmologist with regard to our discoveries and deductions? Or do we fall into the ‘garbage in, garbage out’ trap and fail to provide optimal and potentially valuable diagnostic information?**

**The following, given that my interest is in ocular pathology, are my opinions and approaches to this problem, which I understand may not be shared by busy surgical pathologists without such an inclination.**

**First, I do attempt to find out the patient’s clinical history, preferably before beginning the pathological examination but necessarily before finalizing the pathology report, so as to assure myself that any relevant clinical questions have been addressed. It also demonstrates to the clinician(s) that there is value in the pathological evaluation of these specimens and that we are actively involved in the patient’s care.**

**Second, I am not always successful in my attempts. Then what? It is helpful at this point to know what the indications are for enucleation in general, not necessarily just the ‘blind, painful’ eye. Several large series of ocular specimens have been reported and some of the more recent are summarized in Table 1.<sup>1-13</sup> In general, the more common reasons for enucleation of an eye are: penetrating trauma, neoplasm (usually intraocular but occasionally epibulbar), severe inflammation (endophthalmitis or panophthalmitis), end-stage or absolute glaucoma, and so-called phthisis bulbi. The percentages within these general categories vary**

depending on the clinical practice focus and patient population. In my personal experience in association with a university-based general ophthalmology program and a hospital with a level 1 trauma emergency department, the traumatic and other non-neoplastic cases far outweigh the tumors. Some authors have noted a decrease in frequency, and therefore numbers, of enucleations over the past 30-50 years due to improved therapies of the underlying etiologies.<sup>9,11</sup>

**Table 1: Reasons for enucleation (%)**

Population	Germany <sup>1</sup>	Poland <sup>2</sup>	UK <sup>3</sup>	India <sup>4</sup>	US <sup>5</sup> (Mayo)	China <sup>6</sup>
Date range	1980-1990	1982-2002	1984-2003	1995-2005	1990-2000	2003-2006
N	1146	367	285*	48	646*	1375
Trauma	37.4	36.0	22.1	4.2	11.3	19.9
Neoplasm	19.6	20.7	18.9	16.7	48.2	28.5
Phthisis		9.0	11.2	6.3	11.7	36.4
Glaucoma		19.6	17.2		12.8	10.1
Infection/ Inflammation	7.0	8.1	11.2	39.6	7.1	1.7
Retinal disease	17.1		9.5		8.6	
Corneal disease				14.6		
Surgical complication	14.1					

\* Eucleation and evisceration specimens

Enucleations for neoplasms of the eye are identified as such when submitted for pathological examination and therefore are not included in this discussion other than to say that rarely a clinically undiagnosed intraocular neoplasm may be discovered in an otherwise 'blind, painful' eye. For this reason alone it is important to examine such specimens carefully both grossly and microscopically. Although the risk of such an occurrence is low and has dropped in recent years with the advent of better clinical imaging tools (e.g. ultrasound) of eyes with opaque media, such a scenario was reported in 8 of 2358 (0.34%) enucleation specimens gathered from 1981-1995 in one large series.<sup>14</sup> In three of those cases, diagnostic ultrasound had been performed but failed to detect the intraocular melanoma. In my personal experience with over 500 enucleations 'blind, painful' eye in a twenty year span, I have found only two cases; one case of unsuspected uveal melanoma in an evisceration specimen and one case of unsuspected retinal pigment epithelial adenocarcinoma in a phthisical enucleation specimen.

Likewise, enucleations for acute traumatic injury or acute endophthalmitis are usually categorized as such or are easily recognizable as such on gross examination. Again, however, they merit careful attention, for medicolegal reasons or for discovery of histopathological signs of sympathetic ophthalmia in the former, and for the presence of infectious agents in the latter.

Sympathetic ophthalmia is a fortunately rare but potentially blinding granulomatous inflammatory response, involving both eyes, following penetrating

injury to one eye.<sup>15,16</sup> A putative, as yet unidentified, antigen (or antigens) is exposed to the systemic circulation by the injury, and elicits a T-cell-mediated response. It is postulated that if the damaged ('exciting') eye is enucleated within two weeks of the injury or the onset of inflammation, the immune response is abrogated and the fellow ('sympathizing') eye spared. However, sympathetic ophthalmia has been reported to have developed within five days after injury. It is to my mind the single most important question to be addressed when faced with an eye enucleated for penetrating trauma.

Clinical features of sympathetic ophthalmia include the usual features of uveitis: keratic precipitates on the corneal endothelium, ciliary flush, cells and flare in the aqueous humor, posterior synechiae (adhesions between iris and lens, cells in the vitreous, retinal vascular sheathing and yellow-white subretinal infiltrates known as Dalen-Fuchs nodules. If the inflammation is severe, an exudative retinal detachment may supervene and obscure visualization of the subretinal infiltrates. In one recent study of 40 cases, anterior segment signs were absent on initial presentation.<sup>18</sup>

The sine qua non histopathological feature of sympathetic ophthalmia is the presence of non-necrotizing granulomatous inflammation within the choroid, classically sparing the choriocapillaris. This sparing is not universal, but is cited as the main histopathologic distinguishing sympathetic ophthalmia from another granulomatous choroiditis, Vogt-Koyanagi-Harada syndrome (VKH), with which it shares many clinical features as well.<sup>19</sup> Other granulomatous inflammatory processes must also be considered in the histopathological differential, including mycobacterial and fungal infections, sarcoidosis, and phacoantigenic endophthalmitis. The inflammation in sympathetic ophthalmia is usually diffuse, although occasionally discrete granulomas are present. Aggregates or dispersed epithelioid histiocytes, sometimes with multinucleated giant cells phagocytosing melanin pigment, characterize the granulomatous foci. Macrophage-rich inflammatory cell aggregates at the level of the retinal pigment epithelium correspond to the Dalen-Fuchs nodules, characteristic, but not pathognomonic, of sympathetic ophthalmia. Presence of eosinophils within the inflammatory infiltrate is thought by some to be the earliest histopathologic finding in sympathetic ophthalmia, and eosinophils are more prevalent in severely inflamed cases and in those patients without prior corticosteroid therapy. The lymphocytes present within the uveal tract are, as expected, predominantly T-cells on immunohistochemical staining.

Treatment of sympathetic ophthalmia is with aggressive corticosteroid therapy at the earliest sign of uveitis of uveitis in the fellow 'sympathizing' eye. Severe or refractory cases may require more potent immunosuppressive agents such as cyclosporine A.

Other pathologic findings attributable to trauma include hyphema (hemorrhage into the anterior chamber) with blood staining of the cornea, angle recession, Vossius ring, glaukomflecken, vitreous hemorrhage, retinal detachment with

intraretinal hemorrhage, necrosis, and full-thickness disruption, hemorrhagic choroidal detachment and penetrating laceration of the cornea and/or sclera.

Blood staining of the cornea is a sequela in less than 10% of traumatic hyphemas, but is present in a significantly higher percentage of severe ('8-ball') hyphemas, in which there is a sustained elevation of intraocular pressure. Corneal endothelial dysfunction or loss may allow blood staining at normal pressure levels. The cornea becomes diffusely yellow-tan, more intensely centrally. The opacification may last for years, and clears gradually from the periphery toward the pupillary zone. Histopathologically, corneal blood staining is characterized by innumerable minute red hemoglobin fragments, greater centrally than peripherally, which may involve the cornea transmurally.<sup>20</sup> Descemet's membrane and Bowman's layer are relatively spared. With time keratocytes, and possibly macrophages, phagocytose the hemoglobin and hemosiderin deposits appear, greater in the posterior central stroma. Necrosis and dropout of keratocytes are common

Angle recession is a tear in the anterior face of the ciliary body, between the insertion of the iris root and the ciliary attachment to the scleral spur. It is seen most commonly after blunt trauma to the eye.<sup>21</sup> With anterior-posterior compressive force, the eye expands at the equator, stretching the ciliary body. The tear causes the plane of the iris to move posteriorly, making the anterior chamber appear deeper (recessed). Glaucoma may be a long-term complication of angle recession, often not manifest unless many years after the injury. It is believed that the trabecular meshwork may be subclinically damaged by the injury and with time the resultant scarring causes decreased aqueous outflow and elevated intraocular pressure.

Another manifestation of an anterior-posterior compressive blow is a Vossius ring, an imprinting of melanin pigment from the iris pigment epithelium onto the anterior lens capsule. A similar appearance may be seen in postmortem eyes due to autolysis, so one should be circumspect in rendering that diagnosis.

Traumatic retinal detachment is a common sequela of penetrating trauma, and may result in permanent visual loss even if repaired. Due to their high metabolic demand supplied by the choriocapillaris and not the retinal circulation, retinal photoreceptors begin to degenerate quickly in retinal detachment. On histopathologic examination, this is seen as loss of outer segments and blunting of inner segments, progressing to complete loss of both outer and inner segments and dropout of nuclei in the outer nuclear layer. Clues to distinguish artifactual detachment of the retina as a function of fixation and processing from true retinal detachment are outlined in Table 2 below.

Table 2: True vs. artifactual retinal detachment

FINDING	TRUE RETINAL DETACHMENT	ARTIFACTUAL RETINAL DETACHMENT
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<b>Subretinal space</b>	<b>Eosinophilic/hemorrhagic fluid; +/- macrophages</b>	<b>Optically empty</b>
<b>Photoreceptor outer segments</b>	<b>Degenerated or absent; no adherent melanin pigment granules</b>	<b>Intact (unless delayed fixation); adherent melanin pigment granules at apices of outer segments of rods and cones</b>

**Hemorrhagic detachment of the choroid is also a common complication of penetrating trauma. The choroid is bound to the sclera only at the optic nerve head and at the vortex veins, so that hemorrhages and effusions separating the two layers occur not infrequently when the eye wall is penetrated.**

**An interesting if incidental finding in some cases is the presence of foci of extramedullary hematopoiesis within the choroid. It is not thought to be marrow embolism but rather recruitment of progenitor cells with subsequent proliferation. Although not well described in the literature as a function of trauma, it is nevertheless a not uncommon finding in eyes with penetrating injury.**

**This then leaves those enucleation specimens most likely to arrive in the pathology laboratory with the label ‘blind, painful’ eye. They are often the end-stage result of chronic disease or longstanding inflammation, whose signature features may be masked by secondary degenerative changes. Some etiologies may still be deduced by gross examination, such as chronic open-angle glaucoma and its characteristic deeply excavated, ‘beanpot’ optic disc or chronic retinal detachment with residua from attempts at repair such as extrascleral buckle or intravitreal silicone oil. Others, such as neovascular glaucoma associated with retinal ischemia as in proliferative diabetic retinopathy or retinal vein occlusion, may be more subtle and discoverable only on careful microscopic examination. Finally, there are the cases where secondary changes obscure any identification of the original etiology, and a descriptive diagnosis is then the only one possible.**

**The term phthisis bulbi is used clinically to describe a shrunken, hypotonous blind eye. Strictly speaking, the definition of phthisis bulbi is a shrunken eye with complete disorganization of intraocular contents. Since the disorganization is often not complete in some of these cases, the term atrophica bulbi may be preferred for a pathologic diagnosis.**

**External examination of a phthisical eye reveals a squared eye 8-10 mm smaller than normal in overall dimensions. The squaring is likely due to the traction exerted by the four rectus muscle insertions on the hypotonous globe. The cornea is smaller (2-4 mm) than normal and is often completely opaque and/or vascularized. Band keratopathy (a white zone corresponding to the interpalpebral fissure due to calcification of Bowman’s layer of the cornea) is a common occurrence. Opening the eye may be impossible due to metaplastic bone formation within the eye, necessitating decalcification before internal examination. Once the internal contents**

are revealed, there is often retinal detachment and calcified cataract or evidence of a prior cataract extraction. Prolonged retinal detachment leads to retinal atrophy (total loss of normal architecture) and/or gliosis. The Muller cells and astrocytes in the retina may proliferate to tumoral proportions, a condition known as massive retinal gliosis.<sup>22</sup> There may be significant nuclear atypia within the astrocytes, presumably as a degenerative phenomenon. Although massive retinal gliosis both grossly and histopathologically may be worrisome for a true neoplasm, no case with aggressive biological behavior has been reported to date. Giant drusen are also common in longstanding retinal detachment. Drusen are dome-shaped to placoid PAS-positive deposits beneath the retinal pigment epithelium and within Bruch's membrane. Giant drusen are often calcified. In certain conditions they may predispose to microscopic breaks in Bruch's membrane and allow subretinal neovascularization to occur.

The retinal pigment epithelium proliferates in a variety of ways in phthisical or otherwise chronically debilitated eyes. At the ora serrata it may form a densely pigmented plaque circumferentially ('ringschwiele') in longstanding retinal detachment. It may also assume tumoral dimensions posteriorly, again with atypical nuclear features, and be difficult to distinguish from (albeit rare) a neoplastic proliferation (adenoma or adenocarcinoma).<sup>23</sup> More commonly, the retinal pigment epithelium appears to undergo a metaplastic transformation to produce either collagenous tissue or bone.<sup>24</sup> The degree of bone formation may be such that a circumferential thin layer of bone encompasses the internal contents of the eye like an eggshell, or once again a tumoral mass, of bone with marrow spaces, may fill the eye. Osseous metaplasia of the retinal pigment epithelium must be distinguished from an osseous choristoma of the choroid, which usually occurs in a peripapillary location in women. Only one report of osteosarcoma within a phthisical eye has been reported, perhaps arising from osseous metaplasia of the retinal pigment epithelium.<sup>25</sup>

The degree and hyalinization of the fibrous or fibrovascular tissue proliferation in the vitreous cavity and/or anterior and posterior chambers is indicative of a longstanding degenerative process. Another common finding is migration of corneal endothelium along the anterior chamber angle and onto the surface of the iris. If present long enough, basement membrane will be deposited by the endothelial cells, and the condition may be termed 'descemetization' of the angle and iris. Similar histopathological findings may be seen in iridocorneal endothelial (ICE) syndrome, a unilateral occurrence predominantly in young adult to middle-age women associated with glaucoma.

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**Sebaceous Gland Carcinoma of the Ocular Adnexae**

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**Review of Eyelid Anatomy**

Upper lid longer- rectangular configuration, tarsal plate much longer,  
contains more meibomian glands

Lower lid- shorter, triangular configuration, shorter tarsal plate

Layers: Skin (epidermis and dermis)  
Subcutaneous tissue  
Orbicularis muscle (elliptical sheet of concentrically arranged fibers)  
Pretarsal plane (vessels and nerves)  
Tarsal plate (flat semilunar plates of dense collagenous tissue-  
provide rigidity)  
Palpebral conjunctiva- firmly adherent, invaginations- pseudoglands  
of Henle

Glands of the eyelid: Sebaceous (holocrine)  
Meibomian glands- tarsal plate  
Zeis glands (empty in to lash follicles)  
Sweat glands  
Eccrine sweat glands  
Apocrine sweat gland (glands of Moll)  
Accessory lacrimal glands  
Glands of Wolfring (Ciaccio)- superior margin  
of tarsal plate; 2-5 upper, 2 lower  
Glands of Krause- conjunctival cul-de-sac, 42  
glands in upper, 6-8 in lower)

**Ocular Sebaceous Gland Neoplasms**

**Senile sebaceous gland hyperplasia-**

Mature sebaceous lobule, central duct

Frequently misdiagnosed clinically as basal cell. Can occur in caruncle

**Sebaceous adenoma**

Adenomas associated with Muir-Torre Syndrome have distinct lobular  
pattern with prominent basaloid cells at periphery of lobules (see below)

**Sebaceous Gland Carcinoma**

**(Sebaceous carcinoma, meibomian gland carcinoma)**

**Major Predilection for Ocular Adnexa**

75% Periocular

25% extraocular - 70% of the latter involve head and neck- parotid gland

### **Incidence**

Comprises 5% of eyelid malignancies (USA)  
(basal cell 90%; squamous 4%, melanoma-1%)  
Greater frequency in Asia  
Increasing incidence- ??  
increased awareness?, more accurate diagnosis?, aging population?,  
increasing number of Asians?

### **Risk Factors**

Age- generally disease of older individuals (mean age 57-72 years)  
Sex- 70% female  
Race- more common in whites than blacks in USA  
Higher incidence in Chinese (33%) and Indians (40-60% of malignant eyelid tumors)  
Irradiation  
Prior irradiation for germline retinoblastoma; dermatological conditions  
Muir-Torre Syndrome (see below)  
Immunosuppression

### **Site of origin of ocular adnexal sebaceous carcinoma**

Meibomian glands in tarsal plate  
63% in upper eyelid, 27% lower, 5% both  
Zeis glands – 10%  
Caruncle - 5-10%  
From sebaceous glands of pilosebaceous units  
Conjunctiva  
Cases of intraepithelial carcinoma without intratarsal or intradermal component have been reported  
Multicentric origin – 18%  
Lacrimal gland  
Secondary involvement vs primary tumors (v. rare)  
Eyebrow- little mentioned in ophthalmic literature

### **Broad spectrum of Clinical features**

Eyelid nodule  
Diffuse pseudoinflammatory pattern-  
Diffuse unilateral thickening of eyelid  
Unilateral “blepharitis”  
Conjunctivitis or keratoconjunctivitis unresponsive to therapy  
Corneal opacification by pannus  
Pedunculated or papillary lesion  
Cutaneous horn, papillomatous growth from conjunctiva  
Caruncular mass  
Eyebrow mass  
Lacrimal gland mass

Massive invasion of lids, orbit in neglected cases

***Clinical and Pathological Misdiagnosis of Sebaceous Carcinoma is Common!!!***

***Two-thirds of cases are misdiagnosed clinically:***

**Initial Clinical Diagnosis Prior to Referral to Ocular Oncology Service, Wills Eye Institute (Shields et al)**

Sebaceous Carcinoma	32%
Blepharoconjunctivitis	25%
Chalazion	20%
Basal cell carcinoma	13%
Squamous cell carcinoma	10%

**Misdiagnosed clinically as chalazion or chronic blepharoconjunctivitis (Masquerade Syndromes)**

Clinicians should be advised to submit chronic or atypical chalazia to pathology and to biopsy chronic blepharoconjunctivitis that is unresponsive to therapy

***50% of cases are misdiagnosed histopathologically !!!***

**Primary Histopathologic Diagnosis Elsewhere Prior to Referral to Ocular Oncology Service (Shields et al)**

Sebaceous carcinoma	50%
Squamous cell carcinoma	18%
Basal cell carcinoma	8%
Chronic inflammation	5%
Chalazion	2%
Unspecified neoplasm	2%
Unavailable	15%

***Intraepithelial carcinoma is often misdiagnosed as squamous cell carcinoma in situ***

**Histopathologic Features**

**Degree of Differentiation**

Well-differentiated:	Many tumor cells with sebaceous differentiation lipid in center of tumor lobules
Moderately differentiated:	Only few areas of highly differentiated tumor cells
Poorly-differentiated:	Hyperchromatic nuclei, basophilic cytoplasm Anaplastic carcinoma, pleomorphic nuclei, increased mitotic activity, atypical mitoses

**Histologic Patterns**

Lobular pattern:	Well-demarcated lobules of variable size
Comedocarcinoma pattern:	Large lobules with central necrosis, central lipid staining
Papillary pattern:	Papillary fronds of neoplastic cells with foci of sebaceous differentiation
Mixed pattern:	Assess degree of infiltration

### Confirmation of Sebaceous Differentiation

Fat stains (oil red-O) on frozen sectioned tissues

***It is important to reserve wet tissue for possible frozen sections and fat stains if diagnosis is suspected.***

### Immunohistochemistry

No “magic bullet” for sebaceous carcinoma

IHC least helpful in poorly-differentiated cases where it is need most

EMA, CAM5.2, BRST-1: said to distinguish between sebaceous, squamous and basal cell carcinoma (Sinard)

Stains for MSH2, MLF1 may be indicated if Muir-Torre Syndrome is suspected

### Modes of Spread

**Intraepithelial Spread – a characteristic feature:** 47% of cases

A major factor in pseudoinflammatory presentations in conjunctiva

    Pagetoid spread

        Resembles Paget’s disease of breast

        Single cells and nests of tumor cells within epithelium

    Diffuse “Bowenoid” spread

        Diffuse, full-thickness replacement of epithelium

        May have intraepithelial clefts of acantholytic cells that predispose to epithelial sloughing- non-diagnostic biopsies, problem with FS diagnosis

Spread by Direct Extension

    Orbit, sinuses, intracranial cavity

Perineural and lymphatic invasion

    Preauricular and cervical lymph node metastases (23% Rao- AFIP)

Hematogenous metastasis

    Lungs, liver, brain and skull

### Prognostic Factors and Mortality

    2-30% mortality in older series

    Survival improved recently reflecting increased clinical awareness and improved treatment

### Factors associated with Poor Prognosis (Rao et al, AFIP)

    Upper lid origin, size>10mm, meibomian gland origin, symptom for more than 6 months, infiltrative growth pattern, poor sebaceous differentiation, pagetoid invasion, lymphatic, vascular and orbital invasion.

### Treatment

    Complete surgical removal

Full-thickness eyelid resection (frozen sections may be difficult to interpret)  
 Map biopsies to determine extent of intraepithelial tumor (10-14)  
 Supplemental cryotherapy and topical chemotherapy  
 Orbital exenteration – cases with unresectable orbital invasion  
 Radiation for palliation of advanced cases  
 Sentinel node biopsy recommended by some

### **Muir-Torre Syndrome**

Association of cutaneous sebaceous gland neoplasms, typically sebaceous adenomas and carcinomas and multiple keratoacanthomas with gastrointestinal and other carcinomas  
 Autosomal dominant  
 Caused by mutations in DNA mismatch repair genes MSH2, MLH1, MSH6  
 Skin lesions precede internal cancer in 22%, follow in 56%, concurrent -6%  
 GI tumors in 61%, GU 22%; usually indolent, low-grade visceral malignancies; may be multiple  
 Immunohistochemistry shows absence of MSH2, MLH1 or MSH6 in sebaceous neoplasms and internal cancers

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**2008 Ophthalmic Pathology Companion Meeting USCAP****An Overview of Ocular Cytology**

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## Take-Home Points:

- The majority of ocular specimens received are aspiration cytologies
- Indications for external exfoliative cytology of the eye are usually infectious or post-treatment follow up of malignancies
- Initial triaging by liquid cytology of vitrectomy specimens and anterior chamber taps is very helpful to reach a diagnosis
- A short panel in flow cytometry is used to diagnose intraocular lymphoma
- Specific triaging for molecular diagnosis (PCR for HSV, CMV, HZV, Toxoplasma or gene rearrangement in lymphomas), vitreous ELISA for toxocara, cultures in fungal, mycobacterial or anaerobic bacterial infections is necessary to reach diagnosis in small samples.

*Conjunctiva and Cornea*

Cytology specimens received in the ophthalmic pathology service are both exfoliative and by aspiration. Although exfoliative cytology is easier to obtain they are only performed seldom and most of them are part of obtaining material for cultures. The reason for such a rare specimen is that the same procedures (anesthesia, surgical settings, etc) are necessary for a cytology than for a biopsy of the conjunctiva or corneal epithelium and the later usually involves removal of the lesion. A type of surface cytology is the impression cytology that requires a biopore membrane to obtain the specimen from the surface of the eye. This technique also requires an specific processing technique to transfer cells to the slides. Thus, there are few indications for smears of the conjunctiva or cornea and they include:

- Infectious ulcers (suspecting parasites or fungus)
- Follow up of squamous cell carcinoma in situ and melanoma of the conjunctiva after topical chemotherapy

The slides may be stained with the preferred stain for the cytopathologist to interpret the findings but it is recommended to use either Papanicolaou or a PAS

stain when parasites or fungal organisms are in the differential and only one slide is available.

Acanthamoeba keratitis is characterized by:

- Soft contact lens wearer
- Warm water lakes, swimming pools
- Types: A. castellani and A polyphagia
- Severe eye pain
- Ring infiltrate
- Culture with blood agar layered with E. coli
- Cytology: cystic organisms with thick capsule

#### *Anterior Chamber and Vitreous:*

Normal vitreous is mostly acellular as it is composed of 99% water and the remainder by very few cells (macrophages), avascular and [collagen](#) fibers with [hyaluronic acid](#) . Aqueous humor is 99% water as well and contains proteins, glucose and other soluble nutrients but no cells. Thus, any cellular infiltrate seen in these specimens represents a significant and pathologic finding.

The most frequent specimens received for diagnosis are those from the vitreous or anterior chamber. Vitrectomies are performed daily for many indications and most are not submitted for cytologic analysis in most practices. The indications for submitting the material for diagnosis include:

- Granulomatous uveitis
- Non-granulomatous uveitis with an atypical presentation
- Suspicion of lymphoma
- Atypical necrotizing retinitis
- Atypical presentation of Toxocariasis
- Endogenous endophthalmitis

For diagnostic procedures it is recommended to obtain a sample of undiluted vitreous previous to the vitrectomy procedure to use for specific diagnostic tests. This sample is usually obtained using a 25-30 gauge needle connected to an insulin syringe. The amount of vitreous varies from 0.25-1.00 ml with an average of 0.50 ml.

The vitrectomy procedure includes exchange of vitreous with balance salt solution and the resulting specimen received includes de admixed washings in a bag or a cassette connected to the vitrector. The amount will vary accordingly to the procedure (5-20ml). If endophthalmitis is strongly suspected pre-operatively a portion of the washings are usually submitted directly from the OR to the microbiology laboratory. Thus, the final specimen received in the cytology laboratory would be smaller. It is advisable to inquire about this before using the

washings for other purpose to avoid using all the specimen and not having cultures.

### Lymphoma

Primary intraocular lymphoma presents frequently masquerading as a uveitis. It could present as unilateral or bilateral involvement. In many instances the misdiagnosed intraocular lymphoma is treated as one of the inflammatory conditions with corticosteroids or with antiviral medication. Primary lymphomas are large B-cell type involving the vitreous and retina. Most cases of intraocular lymphoma involve the brain carrying a dismal prognosis. Secondary intraocular lymphoma usually involves the choroid and may be large B or T cell type, or other types of lymphomas. Clinical history and correlation with immunophenotypic findings is essential for the diagnosis. In some cases, it is preferable to sample the vitreous for diagnosis in patients with CNS and ocular involvement of lymphoma than the CNS. The importance of accurate diagnosis is underscored as treatment will be driven by the cytology/immunophenotypic diagnosis.

### Endophthalmitis

Intraocular inflammation may be devastating for vision preservation as the retina – the sensory layer of the eye – is nonrenewable and very sensitive to enzymatic digestion. In addition, the vitreous cavity and intraocular chambers are surrounded by the sclera which is not distensible or permeable making the process more severe. For all these reasons a prompt and accurate diagnosis is necessary to prevent loss of vision. Treatment may be implemented before, during and/or after vitrectomy to prevent the damage. Endophthalmitis is classified as endogenous and exogenous. Exogenous types are associated with trauma, corneal ulcer or surgery and usually start in the anterior segment. Endogenous endophthalmitis is associated to embolism of infectious organism from the originating site (blood, abscess, ulcerative colitis, ulcerated internal tumors, invasive surgical procedures of other organs, IV drug abuse, etc) to the uveal tract or less likely retina/vitreous. In many occasions the primary site of infection is unknown or relatively remote in the history of the patient (> 15 days). Fungal infections predominate in this subtype and they may have an indolent presentation mimicking a granulomatous uveitis. Consideration of this differential diagnosis is important when evaluating the slide for triaging as granulomata may be present but often some neutrophils and the fungal organism are also present.

### Granulomatous vitritis/uveitis

A broad etiology is associated with this entity. Clinically, the presentation may be often indistinguishable from lymphoma or atypical fungal endophthalmitis. The

main differential diagnosis when encountering granulomatous inflammation in the initial slide examined is fungal, sarcoidosis (in adults) and toxocariasis (in children). Other consideration includes toxoplasmosis. Toxocariasis is almost always only seen in children or young adults and the cytologic specimen will show presence of eosinophils. If the slide is stained with Papanicolaou then one should make an effort to identify eosinophils by their morphology rather than their eosinophilic cytoplasm seen in H&E stains. Extremely rare is to find the organisms as it is usually destroyed by the inflammatory component by the time of biopsy. A cell block would be the most helpful next step in these cases because special stains/immunohistochemistry and confirmation of presence of eosinophils.

Anterior chamber taps (aspiration of aqueous fluid) are usually scanty 0.25- 0.50 ml and submitted for cytologic examination to exclude:

- Endophthalmitis
- Leukemia
- Lymphoma
- Retinoblastoma, diffuse type (children)
- Ghost cell glaucoma
- Phacolytic glaucoma
- Granulomatous iritis
- Other

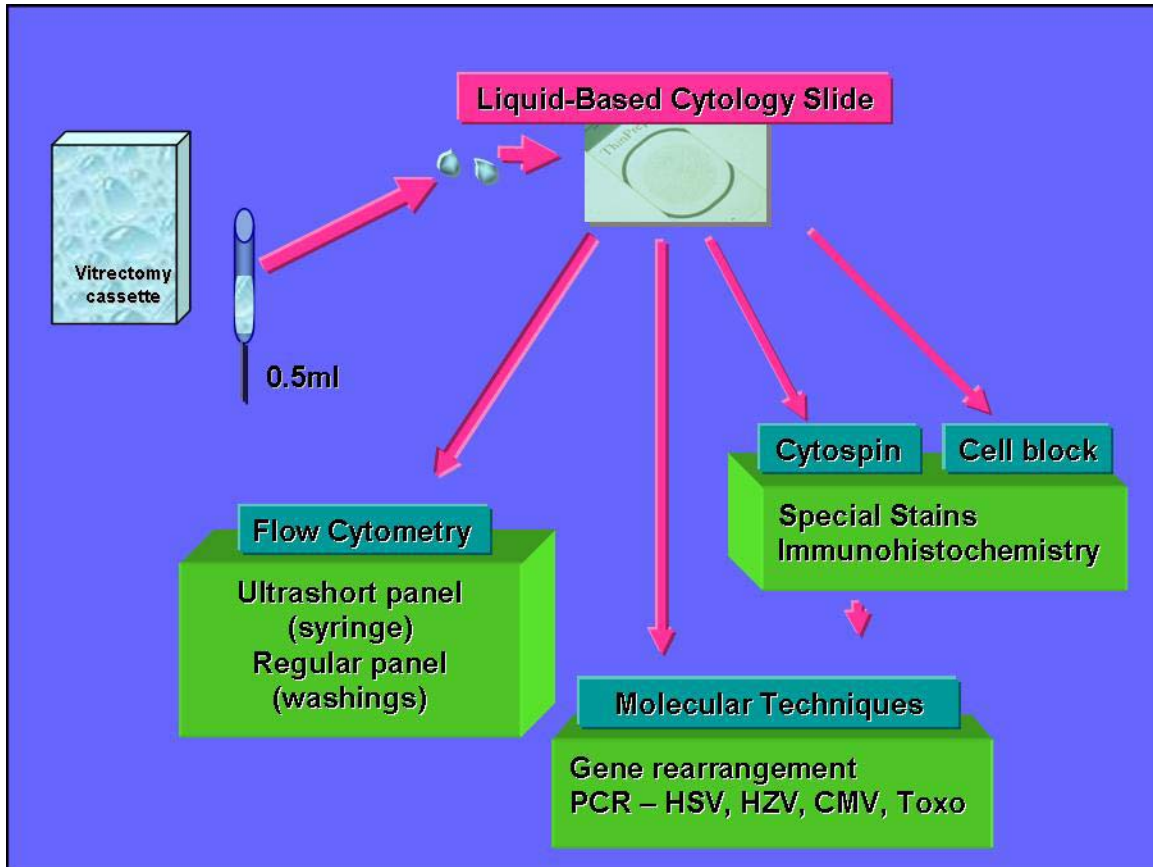
### *Triaging of Specimens*

Triaging of vitrectomy and anterior chamber taps is essential for a timely, and accurate diagnosis. The following is a proposed triaging schema that is used at The Methodist Hospital in Houston to obtain best results (Figure).

It is highly recommended to develop an effective communication with the ophthalmic surgeons that perform these procedures to be prepared. It is desirable that they would communicate in advance and discuss the differential diagnosis with the pathologist.

1. From the insulin syringe (vitreous or aqueous humor) or from the vitreous washings (if this is the only specimen received) use one or two drops to obtain a liquid based cytology slide (preferred for its increased rate of capturing cells and preservation of morphology) or a cytopsin slide.
2. After reviewing the slide decide which study will give more diagnostic information.

3. Most important to differentiate is between possible lymphoma versus granulomatous inflammation and acute inflammation to proceed with the flow chart.



For example: If there are only lymphocytes and specially if they demonstrate atypia (most intraocular lymphomas are large cell lymphoma) the remainder of the specimen should be submitted entirely to flow cytometry (syringe and washings). The cellularity of the flow specimen will determine if a ultrashort panel (to differentiate between B and T-cells only) or a regular panel is used.

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