Ocular manifestations of the phakomatoses

I. Definition of phakomatoses

A. Greek word *phakos* means “spot, lens”

B. Ophthalmologist Jan van der Hoeve coined term phakomatosis in 1920 for three disorders (neurofibromatosis, tuberous sclerosis, von Hippel-Lindau syndrome), which affect the nervous system, eye and skin

C. Conditions commonly included as phakomatoses today
   i. Neurofibromatosis 1
   ii. Neurofibromatosis 2
   iii. Tuberous sclerosis
   iv. von Hippel-Lindau syndrome
   v. Ataxia telangiectasia
   vi. Sturge-Weber syndrome
   vii. Incontinentia pigmenti
   viii. Gorlin syndrome (Nevoid basal cell carcinoma syndrome)

II. Neurofibromatosis 1

A. Inheritance: Autosomal dominant
   i. Mutations in the *NF1* gene that encodes the protein neurofibromin, a GTPase activating protein

B. Prevalence: 1:4,000

C. Systemic manifestations
   i. Tumors
      a. Neurofibroma, MPNST, glioma, leukemia
   ii. Other features
a. Café-au-lait macules, skin-fold freckling, skeletal dysplasia, vascular disorder, learning disability

D. Ocular manifestations

i. Lisch nodules (iris hamartomas)
   a. In ~90% of NF1 patients
   b. Multiple, bilateral, lightly pigmented, raised nodules on the anterior surface of iris
   c. Comprised of pigmented cells and fibroblast-like cells

ii. Glaucoma
   a. In ~50% of NF1 patients
   b. Multiple mechanisms may contribute: infiltration of anterior chamber angle by neurofibroma, malformation or immature development of the anterior chamber angle, secondary angle closure due to infiltration of the ciliary body/choroid
   c. Almost always associated with globe enlargement (buphthalmos)
   d. Frequently associated with iris ectropion

iii. Neurofibromas (eyelid, orbit, uvea)
   a. Choroidal abnormalities detected in 100% of NF1 patients by scanning laser ophthalmoscopy
   b. Ovoid bodies – hyperplasia of Schwann cells around axons, found in choroidal neurofibromatosis

iv. Optic nerve glioma

v. Orbital bony malformations
   a. Absence of the greater and lesser wings of sphenoid

III. Neurofibromatosis 2

A. Inheritance: Autosomal dominant

   i. Mutations in the \textit{NF2} gene that encodes the protein merlin, which has pleiotropic effects

B. Prevalence: 1:40,000

C. Systemic manifestations

   i. Tumors
      a. Schwannoma, meningioma, ependymoma, glioma
D. Ocular manifestations

i. Cataract
   a. Juvenile posterior subcapsular cataracts are found in 80% of NF2 patients
   b. Displaced lens and Wedl/bladder cells are found just anterior to the posterior lens capsule

ii. Epiretinal membrane
   a. In majority of NF2 patients, likely congenital
   b. Immunophenotype and ultrastructural features are most consistent with Muller cell origin

iii. Retinal hamartoma

iv. Optic nerve meningioma

v. Intraocular schwannoma
   a. Arise from the long ciliary nerves

vi. Neurotrophic keratopathy
   a. Vestibular schwannoma → CN VII dysfunction → poor lid closure → corneal damage from exposure

IV. Tuberous sclerosis

A. Inheritance: Autosomal dominant
   i. Mutations in TSC1 and TSC2 genes that encode the proteins hamartin and tuberin, which inhibit mTOR signaling

B. Prevalence: 1:6,000

C. Systemic manifestations
   i. Tumors
      a. Facial angiofibroma, ungual fibroma, cardiac rhabdomyoma, renal angiomyolipoma, subependymal giant cell astrocytoma
   ii. Other features
      a. Cortical tubers, subependymal nodule, hypomelanotic macule, shagreen patch, pulmonary lymphangiomyomatosis, renal nodular hamartomas

D. Ocular manifestations
i. Retinal hamartomas
   a. In ~50% of TS patients
   b. Cells comprising the lesion may have mixed neuronal and glial features

V. von Hippel-Lindau syndrome

   A. Inheritance: Autosomal dominant
      i. Mutations in the VHL gene that encode an E3 ubiquitin ligase, which regulates the cellular response to hypoxia
   
   B. Prevalence: 1:50,000

   C. Systemic manifestations
      i. Tumors
         a. CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumor, endolyphatic sac tumor, broad-ligament cystadenomas
      ii. Other features
         a. Renal cysts

D. Ocular manifestations

   i. Retinal hemangiomas
      a. Multifocal and bilateral

VI. Ataxia Telangiectasia

   A. Inheritance: Autosomal recessive
      i. Mutations in the ATM gene that encode a protein involved in DNA repair
   
   B. Prevalence: 1:30,000

   C. Systemic manifestations
      i. Tumors
         a. Lymphoid malignancy
      ii. Other features
         a. Early onset progressive cerebellar ataxia, immunodeficiency, recurrent infections, oculocutaneous telangiectasias, absent/rudimentary thymus, insulin-resistant diabetes, radiosensitivity

D. Ocular manifestations
i. Conjunctival telangiectasias

ii. Oculomotor abnormalities
   a. Nystagmus, pursuit and saccade abnormalities, strabismus, poor convergence

VII. Sturge-Weber syndrome
   A. Inheritance: Sporadic
   B. Prevalence: 1:50,000
   C. Systemic manifestations
      i. Port-wine stains/nevus flammeus
      ii. Seizures, intellectual impairment, migraine headache, hemiparesis, hemianopsia
   D. Ocular manifestations
      i. Glaucoma
         a. In ~30% of SWS patients
         b. Usually ipsilateral to the port-wine stain
      ii. Diffuse choroidal hemangioma
         a. In ~70% of SWS patients
         b. Ipsilateral to the port-wine stain
         c. “Tomato ketchup” appearance of fundus exam
      iii. Episceral/conjunctival hemangioma
      iv. Iris heterochromia
      v. Buphthalmos
      vi. Retinal pigment degeneration
      vii. Retinal detachment
      viii. Optic disc coloboma
      ix. Cataract
      x. Nevus of Ota

VIII. Incontinentia pigmenti
   A. Inheritance: X-linked dominant
i. Mutations in the *NEMO* gene that encodes a protein critical for NF-κB activation

B. Prevalence: 1:390,000

C. Systemic manifestations
   i. Disturbance of skin pigmentation, leading to a “marble cake” appearance
   ii. Seizures, spastic paralysis, microcephaly, mental retardation
      a. Secondary to compromised vascularization of the developing brain
   iii. Alopecia, anodontia, nail dystrophy

D. Ocular manifestations
   i. Retinal ischemia, leading to reactive neovascularization and fibrovascular scarring
      a. In ~30-40% of IP patients
      b. May be complicated by retinal detachment

IX. Gorlin syndrome (Nevoid basal cell carcinoma syndrome)

A. Inheritance: Autosomal dominant

   i. Mutations in *PTCH1* gene that encodes a transmembrane protein, which inhibits hedgehog signaling

B. Prevalence: 1:60,000-1:260,000

C. Systemic manifestations
   i. Tumors
      a. Multiple basal cell carcinomas, medulloblastoma, fibroma, rhabdomyosarcoma
   ii. Other features
      a. Odontogenic keratocysts of the jaws, hyperkeratosis of palms and soles, epidermoid cysts, multiple nevi, skeletal abnormalities, intracranial ectopic calcifications, facial dysmorphism

D. Ocular manifestations
   i. Hypertelorism
   ii. Exophthalmos
   iii. Rotary nystagmus
   iv. Internal strabismus
v. Congenital cataracts

vi. Orbital cysts

vii. Coloboma of iris, choroid and optic nerve

viii. Microphthalmia

ix. Chalazions

x. Transient milia on the palpebral conjunctiva
Ocular manifestations of the phakomatoses

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Definition of phakomatoses

- Greek word ϕακός, *phakos*, means “spot, lens”
- Ophthalmologist Jan van der Hoeve coined the term phakomatosis in 1920 for three disorders (neurofibromatosis, tuberous sclerosis and von Hippel-Lindau syndrome), which affect the nervous system, eye and skin
Conditions included as phakomatoses

- Neurofibromatosis 1
- Neurofibromatosis 2
- Tuberous sclerosis
- von Hippel-Lindau syndrome
- Ataxia telangiectasia
- Sturge-Weber syndrome
- Incontinentia pigmenti
- Gorlin syndrome (Nevoid basal cell carcinoma syndrome)
Neurofibromatosis 1

- Inheritance: Autosomal dominant
- Prevalence: 1:4,000
- Systemic manifestations:
  - Tumors:
    - Neurofibroma
    - MPNST
    - Glioma
    - Leukemia
  - Other features:
    - Café-au-lait macules
    - Skin-fold freckling
    - Skeletal dysplasia
    - Vascular disorder
    - Learning disability
**NF1** gene encodes the protein neurofibromin, a GTPase activating protein
Neurofibromatosis 1: Ocular manifestations

- Lisch nodules (iris hamartomas)
- Glaucoma
- Neurofibromas (eyelid, orbit, uvea)
- Optic nerve glioma
- Orbital bony malformations
  - Absence of greater and lesser wings of sphenoid
Lisch nodules

- In ~90% of NF1 patients
- Multiple, bilateral, lightly pigmented, raised nodules on the anterior surface of the iris

Atlasgeneticsoncology.org
Lisch nodules

- Iris hamartomas comprised of pigmented cells and fibroblast-like cells

Perlman JI et al. (2005) EOPS
Glaucoma

- In ~50% of NF1 patients
  - Some cases are congenital

- Multiple mechanisms may contribute:
  - Infiltration of anterior chamber angle by neurofibroma
  - Malformation or immature development of the anterior chamber angle
  - Secondary angle closure due to infiltration of ciliary body/choroid

- Almost always associated with globe enlargement (buphthalmos)
Glaucoma

Normal retina

Ganglion cell layer

ganglion cell

Ganglion cell loss
Glaucoma

- Frequently associated with iris ectropion
Choroidal neurofibromatosis

- Choroidal abnormalities detected in 100% of NF1 patients by scanning laser ophthalmoscopy
Neurofibromatosis 2

- Inheritance: Autosomal dominant
- Prevalence: 1:40,000
- Systemic manifestations:
  - Tumors:
    - Schwannoma
    - Meningioma
    - Ependymoma
    - Glioma
The **NF2** gene encodes the protein merlin, which has pleiotropic effects.

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Asthagiri AR et al. (2009) Lancet
Neurofibromatosis 2: Ocular manifestations

- Cataract
- Epiretinal membrane
- Retinal hamartoma
- Optic nerve meningioma
- Intraocular schwannoma
- Neurotrophic keratopathy (vestibular schwannoma → CN VII dysfunction → poor lid closure → corneal damage from exposure)
Cataract

- Juvenile posterior subcapsular cataracts are found in 80% of NF2 patients
Epiretinal membrane

- In majority of NF2 patients, likely congenital
Epiretinal membrane (OS)
Epiretinal membrane
Epiretinal membrane

- Immunophenotype and ultrastructural features are most consistent with Muller cell origin
Intraocular schwannoma

long posterior ciliary nerve
Intraocular schwannoma

S100
Tuberous sclerosis

- Inheritance: Autosomal dominant
- Prevalence: 1:6,000

**Systemic manifestations:**

- **Tumors:**
  - Facial angiofibroma
  - Ungual fibroma
  - Cardiac rhabdomyoma
  - Renal angiomyolipoma
  - Subependymal giant cell astrocytoma
- **Other features:**
  - Cortical tubers
  - Subependymal nodule
  - Hypomelanotic macule
  - Shagreen patch
  - Pulmonary lymphangiomyomatosis
  - Renal nodular hamartomas

Two tubers thicken the cortex and obscure the grey-white junction
**TSC1** and **TSC2** encode the proteins hamartin and tuberin, which inhibit mTOR signaling.

*Orlova KA and Crino PB (2010) Ann NY Acad Sci*
Tuberous sclerosis: Ocular manifestations

- Retinal hamartomas occur in ~50% of TS patients

Syed NA et al. (2004) EOPS
Retinal hamartoma

Syed NA et al. (2004) EOPS
Ataxia telangiectasia

- Inheritance: Autosomal recessive
- Prevalence: 1:30,000
- Systemic manifestations:
  - Tumors:
    - Lymphoid malignancy
  - Other features:
    - Early onset progressive cerebellar ataxia
    - Immunodeficiency and recurrent infections
    - Oculocutaneous telangiectasias
    - Absent/rudimentary thymus
    - Insulin-resistant diabetes
    - Radiosensitivity
ATM encodes a protein involved in DNA repair
Ataxia telangiectasia: Ocular manifestations

- Conjunctival telangiectasias
- Oculomotor abnormalities
  - Nystagmus
  - Pursuit and saccade abnormalities
  - Strabismus
  - Poor convergence
Conjunctival telangiectasias

Normal conjunctiva

Conjunctival telangiectasia
Amphicytes

- Bizarre enlargement of cell nuclei to 2-5 times normal size is found in many organs in AT

Amphicytes in conjunctival epithelium
Is the term phakomatoses still useful?

- Lack of consensus as to which conditions are phakomatoses
- Conditions are due to mutations in distinct genes
- For the most part, clinical features are nonoverlapping
- Commonalities raise similar genetic testing and patient care issues
  - Inherited as autosomal dominant, autosomal recessive or X-linked dominant traits
    (with the exception of Sturge-Weber syndrome, which is sporadic)
  - Chronic
  - Progressive
  - Pleiotropic
Ocular Manifestations of Inflammatory Diseases

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Introduction

A number of inflammatory, non-infectious diseases may involve the eye and the periocular tissues. Often, the systemic disease is already known to the patient and his/her clinician and the ocular manifestations come at a later stage of the disease. However, on some occasions, the ocular manifestations may precede the systemic symptoms and recognition by the ophthalmology and ophthalmic pathologist will allow for an early treatment.

Herein, we will focus on four diseases that might be seen in tissue biopsies by the surgical pathologist. Their clinical and pathological features as well as pertinent differential diagnosis will be discussed.

Sarcoidosis

Sarcoidosis is a multisystem disease of unknown etiology characterized by non-caseating granulomas in various organs. Granulomas most often appear in the lungs (85%) and lymph nodes (34%), but virtually any organ may be involved including the eye (27%) and less commonly the central nervous system (1%). It affects most commonly young adults of both sexes. Incidence is highest for individuals younger than 40 and peaks in the age-group from 20-29 years; a second peak is observed for women over 50. The disease is most prevalent in Northern European countries. In USA, sarcoidosis is more common in African descendent than Caucasians, with annual incidence reported as 35.5 and 10.9/100,000, respectively.

The pathogenesis of this disease is not yet known. The most accepted hypothesis is that in genetically susceptible individuals, sarcoidosis is caused through alteration in immune response after exposure to an environmental, occupational or infectious agent. Studies have shown an increase in B-cell activity with hypergammaglobulinemia in about 50% of the patients. Reduced delayed hypersensitivity is also found in many patients. Immune dysregulation due to persistent low virulence antigen that is poorly cleared by the immune system, leading to a chronic T-cell of the Th1 subtype response, with granulomatous response, has been hypothesized. Medications that increase Th1 response, such as interferon, have been reported to trigger or exacerbate sarcoidosis. Gli-1 oncogene has been found to be highly expressed in patients with sarcoidosis.

The course of the disease is variable, ranging from self-limited acute disease to a chronic debilitating disease that might result in death. Spontaneous remissions occur in 2/3 of the patients, but 10-30% of the patients have more chronic or progressive course.
The mortality rate is 1-6%. Death can be due to pulmonary fibrosis leading to respiratory failure, myocardial involvement leading to cardiac arrhythmias and cardiac failure, CNS involvement, renal insufficiency and liver disease.

The eye may be affected by sarcoidosis in a variety of ways, with the most frequent site being the uveal tract. Obenauf and associates observed anterior granulomatous uveitis in 52% of the 202 patients with ocular involvement; while James and colleagues observed iridocyclitis is 72% of 123 patients with ocular sarcoidosis. Anterior segment involvement is often accompanied by keratic precipitates and posterior synechia. Posterior segment involvement usually accompanies anterior involvement, but it may also occur alone, manifesting as retinitis, choroiditis, chorioretinitis, papillitis or retinal perivasculitis. Posterior involvement may be diffuse. Choroiditis may be localized or multifocal.

Optic nerve and optic nerve head involvement have been reported in about 5% of patients with sarcoidosis. Evidence suggests that patients with retinal and optic nerve involvement are at increased risk to have or to develop CNS involvement. CNS involvement is rare, observed in 2% of all patients, but CNS complications account for 25% of death caused by sarcoid.

Sarcoid may involve the lacrimal gland, giving rise to keratoconjunctivitis sicca. Rarely, it extends beyond the lacrimal gland into orbital soft tissue. This was seen in only 2 of 202 cases (1%) studied by Obenauf et al. Although conjunctival involvement is also infrequent, because of the easy access, it is often biopsied in the search of granulomas to support the diagnosis of sarcoidosis. The yield is approximately 30% positivity in patients with well established diagnosis, 17% positivity in patients with strong clinical suspicion and 0% positivity when sarcoid is only entertained in the diagnosis.

The diagnosis of sarcoidosis is often a matter of exclusion of other diseases including neoplasm. It is made on the basis of signs and symptoms, patient’s age and race and laboratory findings. A definitive diagnosis requires that a biopsy be performed. The typical lesion in the biopsy is characterized by circumscribed epithelioid granulomas with little or no necrosis, and few Langhans giant cells. Giant cells may contain asteroid or Schaumann bodies. A sparse lymphocytic infiltrate might be seen in the periphery of these granulomas, the reason these are referred as naked granulomas.

The differential diagnosis of sarcoidosis includes mainly granulomatous infectious processes such as tuberculosis and fungus infection. Therefore, special stains and tissue cultures for microorganisms must be obtained on routine basis.

Oral corticosteroids are usually the treatment of choice for symptomatic patients. Systemic cytotoxic agents like methotrexate, azathioprine and Chlorambucil may be used in refractory cases. Infliximab, a tumor necrosis factor inhibitor, that neutralizes cytokine TNF-alpha and inhibits it from binding to TNF-alpha receptor, is a promising option for patients with recurrent disease. The visual prognosis of sarcoidosis is usually good.

**Wegener's granulomatosis**

In 1931, Heinz Klinger, a medical student of the University of Berlin, first reported two patients who died of inflammation of the blood vessels scattered throughout the body. Five years later, Friederic Wegener, a German pathologist described three additional patients with necrotizing granulomas involving both the upper and lower
respiratory tract. He was the first one to recognize this disorder as a distinct form of vasculitis.

Wegener's granulomatosis (WG) is an uncommon disease defined by vasculitis and necrotizing granulomatous inflammation involving the kidneys (glomerulonephritis) and the upper and lower respiratory tract (sinuses, nose, trachea, and lungs). Wegener's granulomatosis most commonly affects individuals in the 4th or 5th decade of life. The disease can, however, affect people at any age (age range: 5-91 years), with approximately 15% of cases beginning before 20 years of age. Wegener's granulomatosis strikes both men and women. It is most common in Caucasians (97%) and is rare in African Americans (2%).

Ocular symptoms may be the first manifestation in 16% of patients with Wegener's granulomatosis, while overall approximately half of patients will eventually develop ocular involvement. A common problem in patients with Wegener's granulomatosis is tearing due to nasolacrimal duct obstruction. The orbital inflammation can cause loss of vision, pain, diplopia, proptosis, or orbital bone erosion. Orbital involvement has been reported in 45-70% of patients, and in rare occasions it may precede the detection of the systemic disease. Other ocular manifestations of WG are peripheral ulcerative keratitis and scleritis as well as less commonly uveitis, retinal vasculitis and optic neuropathy.

The histological diagnosis is characterized by the presence of necrobiotic coagulative necrosis, a large number of neutrophils and eosinophils, forming small clusters and intermixed with the necrosis; associated with histiocytic granulomatous reaction around the large areas of necrosis and small vessel vasculitis. Early lesions might not show the full-blown picture (vasculitis, geographic necrosis and granulomatous inflammation). The differential diagnosis is mainly with idiopathic orbital inflammation, in which one should not observe the presence of vasculitis or necrosis.

Wegener’s granulomatosis is considered part of a group of autoimmune disorders known as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, which also includes microscopic polyangiitis, Churg-Strauss syndrome and renal-limited vasculitis. These disorders are characterized by the presence of necrotizing small-vessel vasculitis with the presence of serum autoantibodies directed against neutrophil cytoplasmic constituents, in particular protein 3 (PR3) and myeloperoxidase (MPO). ANCA tests can be performed by both indirect immunofluorescence assay and antigen-specific enzyme-linked immunoabsorbent assay (ELISA). ANCA are believed to play a role a role in the pathogenesis of the vasculitis via activation of neutrophils, but mostly important, they are useful in diagnosis and the management of these disorders. The specificity of c-ANCA in biopsy proven WG has been shown to be 90%. The sensitivity depends on the extent and the activity of the disease. C-ANCA is not detected in most patients at complete remission and rising levels might be indicative of relapse.

The most commonly postulated scenario for ANCA-mediated vasculitis is the interaction of neutrophils and the endothelial cells via cell adhesion molecules, which results in releasing cytokines with damage to the vascular walls. Although many advances have occurred in the understanding of the pathogenesis of WG, so far, it is still not known how tolerance to the autoantigen PR3 is broken and how is the immune response sustained. PR3 induces dendritic cell maturation via the protease activated receptor (PAR)-2 and evokes a strong Th1-type T-cell response in WG. Clusters of PR3 positive cells (neutrophils and monocytes) surrounded by antigen presenting cells, Th1-type CD4+CD28+ effector memory T-cells, maturing B- and plasma cells are found in the granulomatous responses of WG.
lesions. Several important studies have characterized the role of PR3 and PAR-2 in the initiation of this process. These might provide evidences for a more target-specific anti-inflammatory therapy for these patients.

**Necrobiotic Xanthogranuloma**

Necrobiotic xanthogranuloma (NXG), a distinctive dermal and subcutaneous xanthogranulomatous reaction, is a rare form of paraneoplastic syndrome often associated with paraproteinemia. It is a potentially disfiguring disease that can involve the face, trunk or extremities with a particular predilection for the periorbital region.

It was first recognized in 1980 (Kossard and Wilkeman1980). In their report, the authors described 8 patients with multiple xanthomatous plaques and subcutaneous nodules involving the periorbital area, flexures and trunk with a tendency to ulcerate. Six of these patients had IgG monoclonal gammopathy. The ophthalmic features of this disease were later described by Robertson and Wilkelman (1984). Of the 16 patients reported, which included the 8 patients previously described by Wilkeman, 13 had eyelid lesions, 2 had orbital masses, 3 had conjunctival involvement, 2 had keratitis, 3 had scleritis or episcleritis and 3 had anterior uveitis. Eleven of sixteen patients had IgG monoclonal gammapathy, 3 patients had multiple myeloma and one patient had non-Hodgkin’s lymphoma. Since then, several single cases have been reported in the literature.

Clinically, NXG is characterized by large often yellow, indurated plaques sometimes associated with telangiectasia. The lesions often become inflamed leading to superficial ulceration. The most common locations are the periorbital region and thorax. Extensive lesions involving the eyelids may extend into the orbital soft tissues. The clinical differential diagnosis includes mainly xanthelasma and xanthoma, lesions that are not usually indurated. The association of NXG with monoclonal gammopathy is characteristic. Although IgG monoclonal gammapathy represents the most common association, a rare form of IgA gammapathy has also been reported (Fortson and Schroeder 1990), as well as the association with other hematologic disorders such as multiple myeloma, chronic lymphocytic leukemia, lymphoma and other less common diseases such as cryoglobulinemia.

The histopathology is characterized by infiltrates containing mostly macrophages, foamy cells associated with extensive necrobiosis (degeneration of collagen) surrounded by palisading granulomatous reaction. Numerous giant cells, Touton and foreign-body types are usually seen. Cholesterol clefts which have been reported previously do not appear to be as common as initially thought (Finnan 1987). Other findings are lymphoid follicles and a mixture of other inflammatory cells. This particular case was unusual in the finding of small lymphocytic lymphoma, this patient systemic disease, in association with NXG in the same tissue biopsy.

The differential diagnosis includes other necrobiotic disorders, especially necrobiosis lipoidica, subcutaneous granuloma annulare, and rheumatoid nodule. In NXG, the necrobiosis is more extensive than in other diseases and often occurs in broad bands. More important, the clinical presentation differs in each of these lesions. Necrobiosis lipoidica tends to affect mainly pretibial areas in diabetic patients. Granuloma annulare is characterized by papules often in young adults and rheumatoid
nodules are seen in patients with clinically apparent rheumatoid arthritis. Other lesions considered in the differential because of the presence of foamy histiocytes and Touton type giant cells are xanthogranuloma and Erdheim-Chester disease. These entities do not show the necrobiosis that characterizes NXG.

Necrobiotic xanthogranuloma can cause impairing sequela. The cutaneous lesions tend to progress and the course is unpredictable with periods of stabilization, reduction and more aggressive periods with extensive ulceration (Mehregan et al 1992, Ugurlu et al 2000). The treatment is difficult and should include management of the underlying systemic disease and control of the skin lesions. Surgical removal of the lesions is generally not recommended because of the risk of recurrence which was around 42% in a large series (Ugurlu 2000). However, surgery might be necessary to correct scarring and eyelid malfunction. Systemic prednisone and steroid injections have been proposed as alternative forms of treatment, as well as low dose radiation therapy and alkylating regimens.

**Rosai Dorfmann Disease**

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy was first reported in 1969, as a distinct histiocytic disorder in young black men, presenting with bilateral, painless, massive cervical lymphadenopathy with a protracted clinical course, in most cases associated with fever, anemia, neutrophilia, elevated erythrocyte sediment rate and polyclonal gammopathy.

This disorder is most common in the first and second decade of life, but it can occur at any age. Painless lymphadenopathy is the most frequent systemic symptom, involving lymph nodes in the neck (90%), inguinal (26%) and axillary (24%) regions, or mediastinum (15%) in the majority of the cases. Extranodal disease is reported in 43% of patients, some without associated lymphadenopathy. The most common sites of extranodal involvement are skin, nasal cavity and paranasal sinus, eyelid, orbit, bone, salivary gland and CNS.

RDD can involve any part of the eye or orbit, but infiltration of the intraconal space orbital soft tissue is the most common ocular manifestation. Proptosis is the most common symptom; blurred vision, diplopia, dry eye and epiphora can also be seen. On a series by Vemuganti and collaborators, RDD involving the orbit represented 2.3% of all orbital lesions diagnosed in a large tertiary center. Other ophthalmic manifestations include epibulbar masses, compressive optic nerve neuropathy, marginal corneal infiltrates and uveitis. Eyelid thickening is an uncommon manifestation of RDD and in most cases of eyelid involvement it occurs in conjunction with orbital disease. Eyelid involvement as part of generalized cutaneous RDD is very uncommon and it seems affect older patients.

RDD is one of the non-Langerhans cell benign histiocytosis, where predominantly the sinuses or interfollicular area are infiltrated with distinctive histiocytes with round or oval vesicular nuclei, well-defined, delicate nuclear membranes and a single prominent nucleolus. The hallmark of RDD is the presence of lymphophagocytosis or emperipolesis, where viable lymphocytes are located in vacuoles of intact histiocytes. Plasma cells, neutrophils and red blood cells may also be seen within the cytoplasmic vacuoles. The involved histiocytes are activated macrophages that express S100 protein,
HAM 56, α 1 antitrypsin, α 1 chymotrypsin, lysozyme and CD30, but are negative for CD1a. The histopathologic features of RDD in extranodal sites are similar to the nodal disease except for that fibrosis tends to be more prominent and emperipolesis less evident. The differential includes non-specific sinus histiocytosis (lacks emperipolesis and histiocytes are S100 negative), Langerhans’ cell histiocytosis (positive for S100 and CD1a), hemophagocytic syndromes, storage disorder, necrobiotic granuloma, lymphoproliferative disorder, leprosy and metastatic melanoma.

Despite its well-recognized clinical presentation, the precise etiology of RDD remains unknown. The current thinking is that Fas/FasL signaling leading to altered apoptosis may be an important mechanism in the abnormal histiocytic proliferation. A possible viral etiology, related to parvovirus B19 has also been suggested by a recent study.

RDD is relatively unaffected by therapy and it shows a variable presentation. In some cases, the disease has a fast course with complete resolution. In others, it follows a chronic course with episodes of exacerbation and periods of remission. Recurrence might occur later at a different site. Rare cases of death-related to RDD have been reported. Management options include observation, surgical excision or debulking, systemic corticosteroids, chemotherapy or radiotherapy. The treatment of the orbital RDD aims to control functional and cosmetic abnormalities, usually through surgical resections. Recurrent orbital disease or significant residual lesion following surgery may be treated with systemic corticosteroids, radiation or chemotherapy. Chemotherapy has also been used to relieve sight threatening optic nerve compression.

**Selected references**

**Sarcoidosis**


**Wegener’s Granulomatosis**


**Necrobiotic Xanthogranuloma**


Rosai-Dorfmann Disease
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“Ocular Manifestations of Systemic Diseases”

OCULAR MANIFESTATIONS OF INFECTIOUS DISEASES

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HANDOUT

Take Home Points:

- Bacterial, fungal, viral, and parasitic systemic infections may spread to the eye
- Dissemination of these pathogens to the eye is via the bloodstream
- Visual loss is more common in bacterial or fungal endophthalmitis
- Toxoplasmosis is a major cause of ocular morbidity and poor vision after congenital or acquired infection
- Toxocaralisis is an important differential diagnosis in children
Acute retinal necrosis syndrome is associated to viral etiology with confirmation of diagnosis by PCR in aqueous humor or vitreous samples

Indirect mechanisms (eg, HIV-mediated immunosuppression) of some pathogens may lead to opportunistic infections or other ocular manifestations

Successful outcome for patients with ocular infection depends on close collaboration between clinicians, timely identification and treatment of underlying disease, and ophthalmic evaluation and intervention if needed

Introduction:

Systemic infections can affect any part of the eye, and the resultant inflammation and scarring can permanently damage vision. Although many different organisms disseminate via the bloodstream and can directly affect the eye, the most frequent organisms are metastatic bacterial and fungal sepsis. Alternatively, organisms might have secondary effects that could give rise to ocular complications. For example, HIV immunosuppression might lead to opportunistic eye infections or immune recovery uveitis associated with CMV in these patients. In addition, the eye provides a unique window and might be the first opportunity to diagnose underlying systemic infection. More unusual infections and their eye complications are seen in specialized settings, such as critical-care units or in immunocompromised patients (eg, in transplantation or HIV medicine). Knowledge of the complications—eg, endophthalmitis in candidaemia—is mandatory for physicians working in relevant disciplines, including pathologist to assertively and timely make the diagnosis. The eye has several properties that make it very sensitive to infection and further sequela. The intraocular tissues are enclosed by the thick sclera and the vascular uveal tissue, thus, the immune response incited by infection (mostly neutrophilic and macrophagic with enzymatic release) can damage the retina in addition to the direct damage caused by the infectious pathogens. As a result, steroids are often used with antimicrobial drugs to reduce the inflammatory response and thereby limit the damage caused. The healthy eye is protected by tight blood-aqueous and blood-retinal barriers, which limit access to the retina but it is damaged during infection and inflammation. Thus, these barriers become leaky and this becomes critical to the pharmacokinetics of various antiinfection drugs. Prompt and accurate histopathologic, cytologic and/or microbiologic diagnosis of these diseases then turns out to be essential in the treatment of these patients to avoid long
term and unrecoverable damage to the retina and other vital tissue for vision and for life.

**Selected cases of ocular infections in systemic disease and the prefer mode of diagnosis**

**Metastatic endogenous endophthalmitis- Diagnostic cytology/cultures**

Metastatic (endogenous) endophthalmitis occurs when pathogens (mainly bacteria and fungi that cause bloodstream infection and systemic sepsis) disseminate to the eye, leading to intraocular infection. It might arise at the same time as infection at other body sites, which include bone, heart valves, liver, lung, and brain. Alternatively, endophthalmitis could be the only clinically apparent site of infection where initial bacteremia or fungemia has not been recognized or detected. Further investigation of affected patients can identify infection at other sites. Failure to recognize ocular involvement in the treatment of focal infection at other sites can lead to insufficient treatment or eradication of eye infection. Patients might then present with endophthalmitis some time after their initial systemic illness. Although metastatic spread to the eye is a rare complication of sepsis, it can lead to catastrophic visual loss. Early recognition of ocular involvement is essential, because many systemically administered antibiotics penetrate poorly into the eye and a change or addition of other antimicrobial drugs might be needed to control both systemic and eye infections. Aqueous humor or vitreous samples should be treated as STAT specimens to procure the fastest and accurate diagnosis possible. It is suggested that both cytology and cultures with possible PCRs are processed to obtain best results. Two thirds of the bacteria found in these cases are gram-positive- *Streptococcus* spp and *Staphylococcus* spp organisms, but many others such as *Neisseria meningitidis* can also disseminate to the eye. The most frequent underlying problems are endocarditis, gastrointestinal tract infection, and pneumonia. Other less common primary sites of infection include skin abscess, infected joints, and the urinary tract. Patients at high risk of fungemia are those with indwelling central venous catheters, long-term stay in intensive care units, use of broad-spectrum antibiotics, intravenous drug abuse, and neutropenia. The most frequent fungal pathogens found in endogenous endophthalmitis include: *Candida albicans*, *C glabrata*, *C tropicalis*, *C parapsilosis*, *C krusei*, *Aspergillus niger*, and others. Systemic fusarium infections
might also cause endophthalmitis and this organism has been in the rise as causative pathogen of exogenous and endogenous endophthalmitis.

**Acute retinal necrosis and CMV, HZV, EBV, HSV and Toxoplasma – Diagnostic PCR-Cytology**

Acute retinal necrosis (ARN) is an uncommon intraocular inflammatory syndrome characterized by severe and diffuse uveitis, retinal vasculitis, and retinal necrosis. It is typically described to occur in immunocompetent patients, but can also be found in immunocompromised subjects. Varicella-zoster virus (VZV), herpes simplex virus (HSV 1 and 2), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) have been implicated in the etiology of ARN. The diagnosis of ARN is usually suspected based on clinical features but may be included in the differential diagnosis of the masquerade syndrome (lymphoma, Toxoplasma, vs. other). Cytology of the vitreous sample is helpful in differentiating other causes of the masquerade syndrome. The use of polymerase chain reaction (PCR) in aqueous humor samples or better in vitreous samples, is the most useful to identify the etiology of the disease.

Toxoplasmosis, infection with *Toxoplasma gondii*, is the most common cause of infectious uveitis worldwide. Although most eye infections were thought to be acquired in utero, at least a third of patients presenting with active eye disease are now estimated to have been infected postnatally. Although cats are the definitive hosts in which sexual reproduction can only occur, humans can be infected directly by cysts in cat feces and from eating meat from intermediate hosts (chickens, lambs, and pigs) that contain cysts with larval forms of the parasite. Primary toxoplasmosis is generally asymptomatic in immunocompetent individuals, although patients might occasionally experience systemic illnesses, including lymphadenopathy or hepatitis. Symptomatic ocular involvement in primary infection is rare but local ocular reactivation of disease without systemic reactivation is frequent. In primary infection, typical lesions are related to retinitis, have no evidence of previous chorioretinal scarring, and have a mild intraocular inflammatory response. Many lesions are self-limiting and heal, forming characteristic pigmented scars in the retina where toxoplasma cysts are found. Scars can be seen anywhere in the retina, are often unilateral, but can be bilateral. Reactivation of infection from quiescent scars is rare in childhood (whenever infection was acquired) and the mean age of first symptomatic recurrence is 20–25 years.
Active, white lesions form on the edge of scars, with a striking intraocular inflammatory response. The immune response stimulated by active *T. gondii* infections is substantial enough to contribute to retinal damage. Although these lesions are usually self-limiting, combined treatment with corticosteroids and antitoxoplasma drugs is often given if active lesions are close to the optic nerve or macula or if there is a severe intraocular inflammatory response. In immunocompetent hosts, there is no evidence that any of the presently used antitoxoplasmosis drugs have any effect on the natural history of the disease, but drug regimens in general use do vary in their side-effect profiles. Typical symptoms and signs of toxoplasmosis, such as ocular scars, can appear at birth or later in life. Patients with severe immune compromise either because of immunosuppressive drugs or HIV infection might acquire primary toxoplasma infection, but disease is more commonly due to reactivation. For example, in patients with HIV-related disease, 90% of CNS toxoplasmosis is due to reactivation. Patients with active eye lesions present with sore red eyes, or floaters due to the vitritis or visual loss. Additionally, they could also have coexistent cerebral lesions, which can appear as contrast enhancing on CT or MRI scans, causing sixth cranial nerve palsies and papilloedema. Drug treatment for ocular and cerebral toxoplasmosis is the same and lesions will continue to grow without therapy. In immunocompromised individuals these presentation may have a broader differential diagnosis and vitreous cytology with PCR may be necessary for definitive diagnosis and treatment.

**Immune Recovery Uveitis – Differential diagnosis in Cytology specimens/PCR(CMV)**

Immune recovery uveitis occurs only in patients who are receiving potent antiretroviral therapy and whose CD4 T-lymphocyte count has increased (a marker for improved immune function), thus, it is a response against cytomegalovirus within the eye. A simple model to explain some of the features of immune recovery uveitis includes that as immune function improves, a threshold is reached at which the body can mount an intraocular inflammatory response to cytomegalovirus antigens present in the eye. It is known that continued production of viral proteins can occur in cytomegalovirus retinitis lesions that appear clinically inactive. With continued recovery of immune function, a higher threshold is reached at which the immune system inactivates cytomegalovirus, production of antigen then stops, and inflammatory
reactions subside. This simple model does not, however, explain why some patients are reported to develop immune recovery uveitis long after initiation of potent antiretroviral therapy, or why it persists in others. An intriguing theory is that control of cytomegalovirus retinitis is incomplete in some individuals, with subclinical production of virus or viral proteins that continue to stimulate the immune system. Researchers have found persistence of detectable cytomegalovirus in the blood of individuals after the start of potent antiretroviral therapy, despite the apparent inactivity of cytomegalovirus retinitis on clinical examination. This observation suggests the possibility that continuing maintenance anticytomegalovirus therapy during a prolonged period after initiation of potent antiretroviral therapy might reduce the frequency and severity of immune recovery uveitis. Immune recovery uveitis can, however, develop even in patients receiving specific anticytomegalovirus therapy.

**Herpes Simplex Vegetans in Eyelids. Biopsy and Immunohistochemistry**

Cutaneous infection with HSV can occur in immunocompetent or immunocompromised hosts, however the clinical manifestations vary greatly based on the immune status of the patient. The most common cutaneous manifestations of HSV in immunocompromised patients such as solid organ transplant recipients are oral and genital mucosal ulcerations and vesicular lesions; however, they also may present with ulcers that can become confluent, chronic, and granulating. In rare cases, disseminated skin lesions resembling erythema multiforme can develop. Herpes simplex vegetans is a rare variant that can occur in immunocompromised patients. The five published case reports of herpes simplex vegetans describe exophytic, sometimes exudative or ulcerated growths that may mimic malignancy. These have been reported to occur on digits, genitalia and oral mucosa and we have reported the first case in the eyelids. To our knowledge, this is the first report in a patient with a congenital immunodeficiency, occurring as an eyelid lesion. The clinical differential diagnosis for a solid, ulcerating mass in an immunodeficient patient is fairly broad, including mycobacterial and fungal infections as well as malignancies such as squamous cell carcinoma and cutaneous t-cell lymphoma. It is important to biopsy the lesion to make the diagnosis. The pathologic features of herpes simplex vegetans include an intense inflammatory response with granulation tissue, many plasma cells and sometimes eosinophils. The typical viral inclusions are usually seen on the periphery of the lesions, although in our case these cells were seen in the subepithelial tissue and along the hair follicles. Given the intense
lymphoplasmacytic reaction seen with this type of lesion it is important to rule out Epstein-barr virus associated lymphoproliferative disease that can occur not uncommonly in immunocompromised patients. This is easily done by immunohistochemistry. Treatment failure with acyclovir is almost a defining feature of herpes simplex vegetans. The few case reports report various treatment strategies, but all of them describe resistance or treatment failure with acyclovir. Treatment with valcyclovir, foscarnet, famicyclovir and even imiquimod, in one case report, seemed to have better responses. It is unclear how long these patients need to be treated or if recurrence is common on chronic suppressive therapy. One report suggested that herpes-simplex impaired production of interferon-alpha, implied by successful treatment with topical imiquimod.

**Toxocariasis. ELISA in serum and vitreous/cytology**

Toxocara is widely distributed and is acquired mainly by children ages 4 to teens, secondary to contact with puppy dogs and cats or their excreta. Ocular symptoms of infection with toxocara are rarely associated with systemic infection of visceral larval migrans. Current detection of antitoxocara antibodies by ELISA has poor sensitivity, and the titre can be very low or absent in active ocular disease. Thus, ELISA on vitreous fluid samples improves detection especially combined with the results of the ELISA in serum. Ocular involvement is unilateral, the eyes appear quite without conjunctival or ciliary involvement, and the diagnostic feature is a peripheral white mass (snow bank) is often visible. Other ocular features depend on the location of the worm within the eye and the inflammatory response it generates. These include a tractional vitreous band from the optic nerve to the peripheral white mass. In young children, the disease might present as endophthalmitis and can resemble retinoblastoma, but calcification is rare. Treatment is rarely needed because inflammation is often occult and subsides spontaneously. However, in extreme cases the anterior chamber is involved by inflammation or its complications and secondary glaucoma or even ocular atrophy as consequence of the inflammation may occur.

**Orbital Mucormycosis. Biopsy with histopathologic typical findings**

Rhino-cerebral-orbital mucormycosis (zygomycosis) infection is an aggressive fungal infections with a high mortality rate. It has a higher incidence in patients with untreated diabetes, kidney diseases or with
hematological malignancies. Following aspergillosis, mucormycosis is the second most frequent mycosis caused by filamentous fungi. The family of the *Mucoraceae* is divided into the subspecies absidia, rhizopus and mucor. The most typical clinical manifestations are rhino-cerebral, maxillo-facial and pulmonary mucormycosis. Rhino-cerebral mucormycosis starts in the nose or oral cavity infiltrating the paranasal sinuses, the orbit or the brain over the orbital apex or the cribriform plate. The first symptoms are non-specific with headache, fever or rhinorrhea. Frequently, intranasal black necrotic crusts can be found. At the time of presentation, the symptoms often are advanced and patients already show complications like orbital involvement of the disease with proptosis, ophthalmoplegia or worse with intracerebral spread with meningitis or brain abscess. Three clinical stages for mucormycosis infection have been identified: patients with limited sino-nasal disease (clinical stage I), patients with limited rhino-orbital disease (clinical stage II) and patients with rhino-orbital-cerebral disease (clinical stage III). A CT scan is crucial for identification of the bony destruction. MRI provides early detection of meningeal or intraparenchymatous spread and intracranial vascular occlusion. The definite diagnosis can only be verified by histological examination. Hyphae are typical and specific for each fungus. Mucor presents large, broad non-septate hyphae with rightangle branching. The best way to detect is looking at the vessel walls as they are usually either forming a thrombus or invading the wall itself. Many times they can be visible with routing H&E stains and PAS and GMS are confirmatory. Mucormycosis requires early aggressive and extensive surgery of all infected devitalized tissue. If the underlying immune deficiency is not successfully treated, the prognosis is very poor. Especially the orbital apex appears to be an area particularly in danger of further intracranial spread because of numerous potential pathways, like the superior orbital fissure and the optic canal. The addition of exenteration to sino-nasal debridement did not improve patients’ outcome when the state of the underlying disease was poor or not corrected. Nevertheless, aggressive surgical treatment is still recommended, including exenteration of the orbit. Once the endocranium is reached by fungal disease, a craniotomy with debridement should be considered immediately, as well as hyperbaric oxygen therapy combined with antifungal drug treatment.
References:


Learning objectives

1. To discuss the most common malignancies that metastasizes to the eye.

2. To familiarize the audience with the most prevalent clinical presentations and findings.

3. To compare and contrast the different histopathological findings of the most common tumor types.

I. INTRODUCTION

Long-term survival from systemic malignancies continues to increase; therefore pathologists will be confronted with a growing incidence of intraocular and orbital metastatic disease requiring appropriate prompt recognition and diagnosis for patient management. The increased incidence of metastasis to the eye is due to the increase incidence of tumors that metastasize to the eye (lung, breast), a prolonged survival of patients with certain cancers (breast cancer) and increasing awareness among medical oncologists and ophthalmologists of the pattern of metastatic disease.

The mechanism of intraocular metastasis is secondary to hematogenous dissemination of tumor cells. The anatomical ocular arterial supply dictates the predilection of metastatic disease. The posterior choroid, with its rich vascular supply, is the most favored site of intraocular metastases, and it is affected 10-20 times more frequently than the iris or ciliary body. The retina and optic disc, supplied by the single central retinal artery, is rarely the sole site of involvement. Bilateral ocular involvement has been reported in 20-25% of cases, and multifocal deposits are frequently seen within the involved eye. Many patients with ocular metastases also have concurrent CNS metastasis.

Primary tumor sites

The majority to metastatic solid tumors to the eye are carcinomas from various organs. Cutaneous melanoma rarely metastasizes to the eye. Table 1 shows the most common primary tumors that metastasize to the choroid. Breast and lung carcinomas for women and lung and gastrointestinal carcinomas for men most commonly metastasize to the eye and orbit.
Table 1. Primary Sites of Choroidal Metastasis

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (40%)</td>
<td>Breast (68%)</td>
</tr>
<tr>
<td>Unknown (29%)</td>
<td>Lung (12%)</td>
</tr>
<tr>
<td>Gastrointestinal (9%)</td>
<td>Unknown (12%)</td>
</tr>
<tr>
<td>Kidney (6%)</td>
<td>Others (4%)</td>
</tr>
<tr>
<td>Prostate (6%)</td>
<td>Gastrointestinal (2%)</td>
</tr>
<tr>
<td>Skin (4%)</td>
<td>Skin (1%)</td>
</tr>
<tr>
<td>Others (4%)</td>
<td>Kidney (&lt;1%)</td>
</tr>
<tr>
<td>Breast (1%)</td>
<td></td>
</tr>
</tbody>
</table>


Clinical Findings

The clinical features of intraocular metastasis depend on the site of involvement. The clinical features of ocular metastasis may include:
- eyelid or conjunctival mass
- iridocyclitis
- secondary glaucoma
- hyphema (blood in the anterior chamber)
- irregular pupil
- proptosis
- orbital mass
- poor vision
- pain and photopsia

Most patients have a history of systemic malignancy. Some patients however, have no previous history of malignancy. This is especially true of patients with ocular metastasis from the lung. The diagnosis of tumor metastatic to the uvea implies a poor prognosis, because widespread dissemination of the primary tumor has usually occurred. It has been reported that the survival time following diagnosis of metastasis to the uvea ranged from 1 to 67 months, depending on the primary cancer type.

Treatment

The goal in ophthalmic management of ocular metastases is preservation or restoration of vision and palliation of pain. The short-term prognosis for vision is usually good after an individualized therapeutic approach (chemotherapy, hormonal therapy, external beam radiotherapy, or plaque radiotherapy), but the systemic prognosis is poor.

The visual paraneoplastic syndromes encompass several distinct clinical and pathological entities including carcinoma-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and bilateral diffuse melanocytic uveal proliferation (BDUMP). The CAR syndrome affects photoreceptors, MAR is thought to affect bipolar
cell function, and BDUMP targets the uveal tract. Identification of circulating antibodies against retinal proteins (recovering, 23-kDa retinal protein; 46-kDa and 60-kDa retinal proteins) serves to recognize the paraneoplastic nature of the patient's symptoms, which frequently develop before the cancer is diagnosed. Anecdotal therapeutic responses are described after systemic steroids, immunoglobulin injection, and plasmapheresis. Recognition of the visual symptoms and ocular findings should alert to the possibility of cancer and systemic evaluation should be pursued.

II. CASE PRESENTATIONS

CASE NUMBER 1

Chief Complaint: A 70-year-old Asian male patient presented to the New England Eye Clinic with a 3-week onset of rapidly growing lesion of his left upper eyelid with bleeding (picture 1). He denied fever, chills, night sweats, weight or appetite loss, chest pain, back pain, diarrhea, constipation or headache. Warm compresses and erythromycin ointment were applied to the lesion, without any obvious improvement.

Past Medical History: Myocardial infarct in 1986, cardiomyopathy, emphysema, COPD, hypertension, and chronic renal disease secondary to hypertension. He had no previous ocular history.

Social History: He had a 40-pack-year history of smoking, quit in 1986. He had no history of alcohol abuse, and had worked in a laboratory with unknown chemicals. He was married, retired, and lived alone.

Medications: Isosorbide and lisinopril.

Radiology Data: A head CT scan showed a 9 mm x 6 mm left eyelid lesion. No intracranial brain lesion, intracranial hemorrhage or edema was found.

General Impression and Differential Diagnosis: A tissue biopsy was performed of the eyelid lesion. The differential diagnosis included among others basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, lymphoma, Merkel cell carcinoma, Kaposi’s sarcoma, metastatic tumor, neurofibroma, sarcoid nodule, SLE nodule, hemangioma, and chalazion.

Histopathological Evaluation: A predominantly subconjunctival epithelial tumor mass with focal surface erosion is present. A tumor showing solid growth pattern with round to oval or fusiform population of cells, scanty cytoplasm, hyperchromatic finely granular nuclei and inconspicuous nucleoli was present. Numerous mitotic figures, apoptotic cells and focal necrosis was also found. Immunohistochemistry staining showed the tumor cells immunoreactive to CK7, pancytokeratin, EMA, synaptophysin, and TTF-1 (thyroid transcription factor 1). They were negative for CEA, CK20, S100, Melan A, HMB45, CD45 and chromogranin. The histopathological features coupled with the immunohistochemical profile favored a metastatic carcinoma, highly suggestive of lung origin.

Staging and Treatment: A CT scan of the chest showed a right upper lobe nodule anteriorly, soft tissue fullness in the superior mediastinum and below the left upper lobe bronchus. The changes were consistent with lung tumor with possible malignant lymphadenopathy. There were also bilateral lung apices scarring, and radiolucencies consistent with bullous disease and emphysema. Multiple calcified tiny nodules were present, probably representing old TB. A PET scan confirmed a lung lesion and mediastinal adenopathy, adrenal, distant lymphadenopathy and retropharyngeal involvement.
The patient was treated with six cycles of chemotherapy (etoposide, vincristine) for 5 months. He developed a superior vena cava syndrome, a residual lung nodule and mediastinal adenopathy as well as a large adrenal mass. He died nine months after the initial diagnosis.

**Figure 1. Clinical Presentation**

**CASE NUMBER 2**

**Chief Complaint:** A 74-year-old man presented with episodic blurred vision in the right eye of two months duration. In addition, he noted a supero-nasal visual field defect when closing his left eye. The patient had no monocular complaints.

**Clinical Examination:** On ophthalmological examination his visual acuity was 20/400 in the right eye and 20/25 in the left eye. Funduscopic examination disclosed an infero-temporal amelanotic choroidal tumor with associated sub-retinal fluid. A B-scan showed a vascular dome-shaped lesion of medium to high internal reflectivity measuring 7.6 x 8.4. x 3 mm (Figure 1). A fluorescein angiogram showed early fluorescein uptake by the tumor with a mottled hyperfluorescent pattern.

**Past Medical History:** no significant past medical history was present.

**Radiology Data:** The patient was referred for an oncologic work-up including CTs of the chest and abdomen as well as routine blood work up. These studies were negative for systemic malignancy. A fine needle aspiration of the lesion was attempted but was non-diagnostic.

**General Impression and Differential Diagnosis:** The tumor continued to grow after six weeks of follow up and studies and developed cystic cavities. Based on the funduscopic, fluorescein angiography and B-scan findings, a metastasis was suspected rather than a primary amelanotic choroidal melanoma. Due to continued growth of the neoplasm and negative systemic work-up, the eye was enucleated.

**Histopathological Evaluation:** The globe contained an infero-temporal amelanotic choroidal mass with an overlying and peripheral retinal detachment. Microscopic examination showed a metastatic adenocarcinoma. Immunohistochemistry staining for PSA and PSAP were positive in the tumor cells. The findings were consistent with a prostatic primary.

**Staging and Treatment:** A serum PSA (which had not be evaluated prior to the enucleation) was markedly elevated at 640 ng/ml (normal <5 ng/ml). A bone scan revealed metastatic disease of the entire axial skeleton. Prostatic biopsies confirmed the diagnosis of adenocarcinoma. The patient underwent radiation therapy and chemotherapy.
Selected References


