Ophthalmology Grand Rounds

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May 5, 2011

History

- CC: “My eyes are swelling shut.”
- Pt is a 30 yo AA female who presented to Brooklyn Hospital ED with c/o bilateral eye pain, redness and swelling x 2 weeks. Pt states symptoms began in her left eye and then affected the right eye. She also noted “seeing double” at times. Pt was given a Rx for antibiotics and discharged with outpatient follow-up.
- After visit to PMD, the pt was referred to Ophthalmology at LICH for further evaluation.

PATIENT CARE, INTERPERSONAL SKILLS

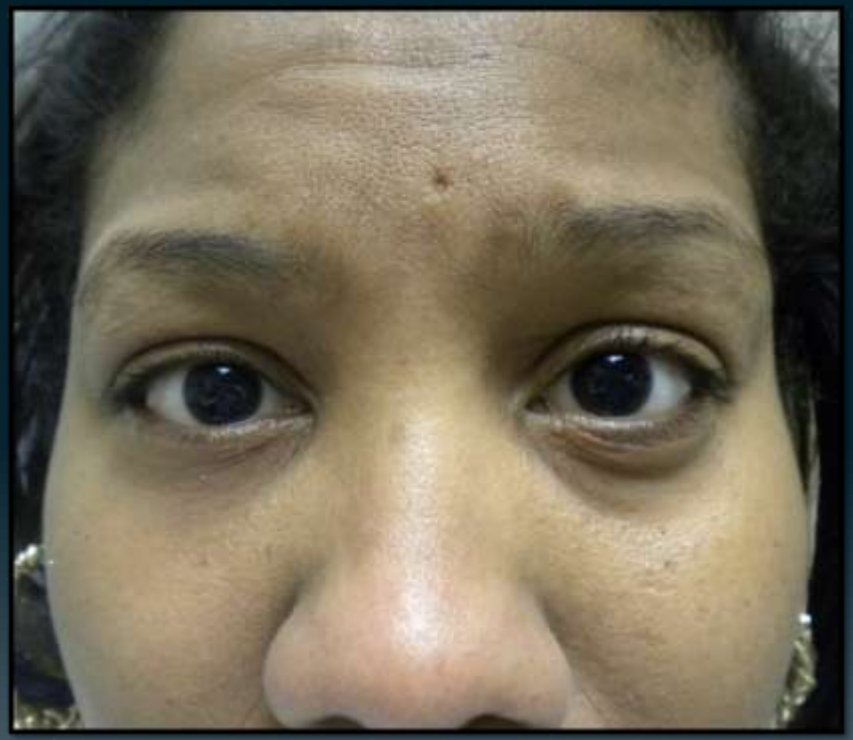
History

- PMHx: Obesity
- POHx: No surgery/no trauma
- FHx: No blindness/no glaucoma
- All: NKDA
- Gtts: None
- Meds: recent Abx use (cannot recall meds)

PATIENT CARE, INTERPERSONAL SKILLS

Physical Exam I

- HEENT: lacrimal fossa mass OD>>OS, +tenderness to palp OU (OD>>OS)
- DVa sc: 20/20 OU
- P: 4-2 mm OU, no APD
- EOM: full OU +pain; +binocular horiz diplopia in 1° gaze, binocular vertical diplopia in upgaze
- CVF: ftfc OU
- Tap: wnl OU



PATIENT CARE, MEDICAL KNOWLEDGE

Physical Exam II

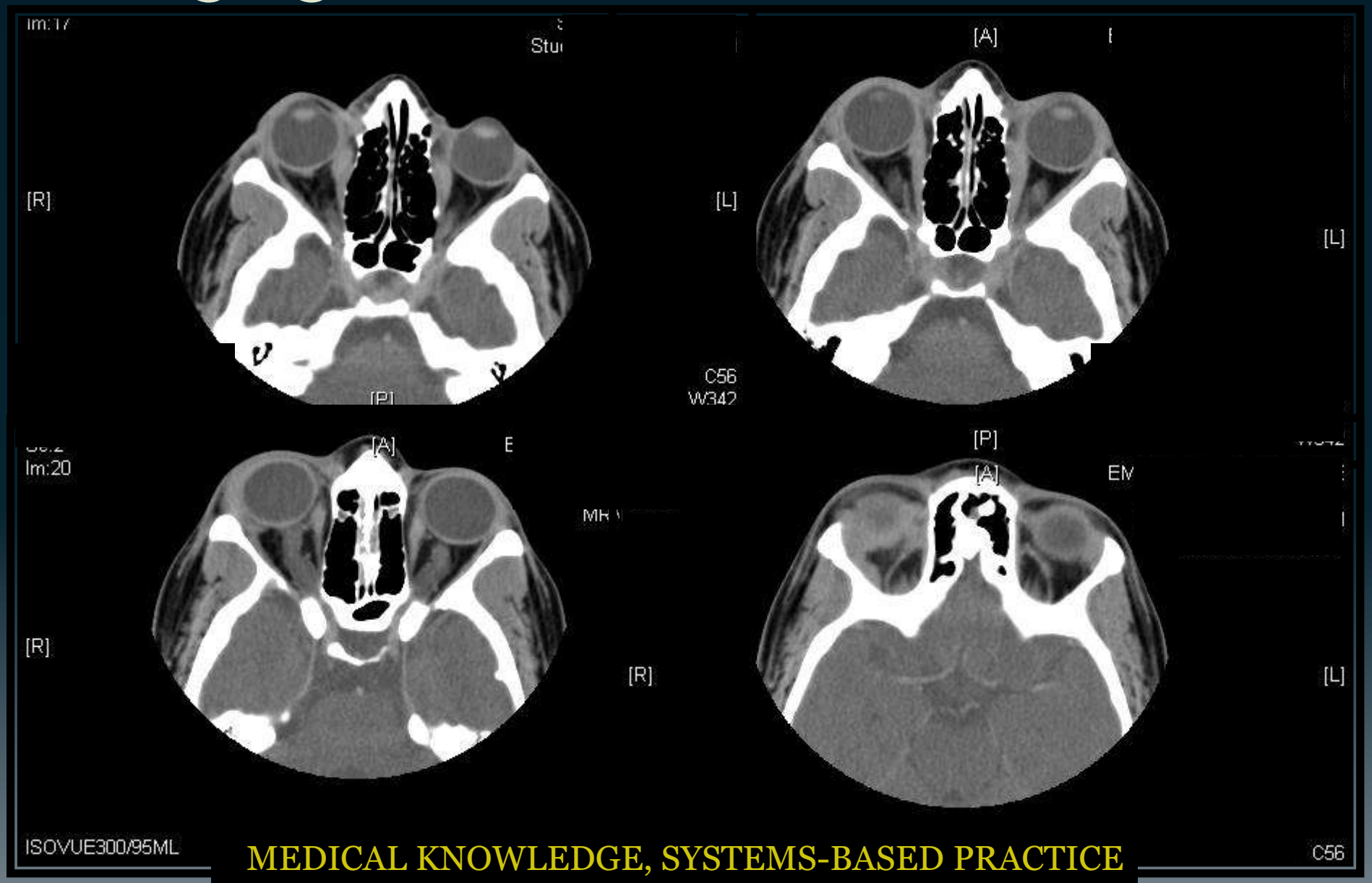
- SLE
  - LLA: mild UL mechanical ptosis OD, trace periorbital edema OU
  - C/S: w/q OU
  - K: clear OU
  - AC: d/q OU
  - I/P: b/r/r OU
  - Lens: clear OU
- DFE
  - Within normal limits
  - Optic nerves - c/d 0.3 sharp/pink OU

Differential Diagnosis

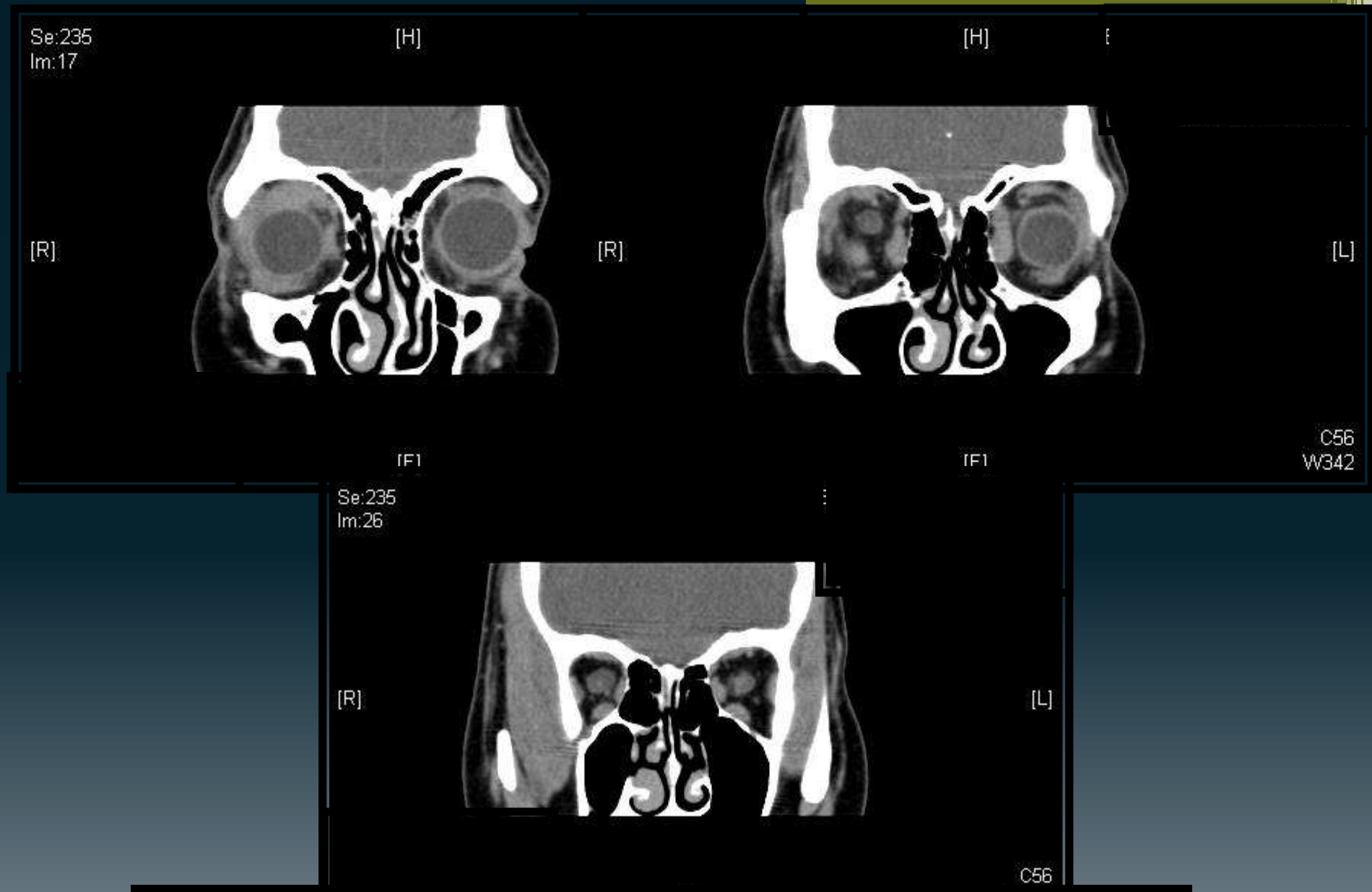
- Infectious?
  - Orbital cellulitis, subperiosteal abscess
- Neoplastic?
  - Metastatic disease, dermoid cyst, capillary hemangioma, optic nerve glioma, lymphoma, lymphangioma, leukemia
- Inflammatory?
  - Thyroid-related orbitopathy, orbital pseudotumor, sarcoidosis
- Traumatic?
  - Orbital fracture, retrobulbar hemorrhage, carotid-cavernous fistula
- Malformation?
  - Congenital, vascular, etc.

MEDICAL KNOWLEDGE

Imaging



MEDICAL KNOWLEDGE, SYSTEMS-BASED PRACTICE

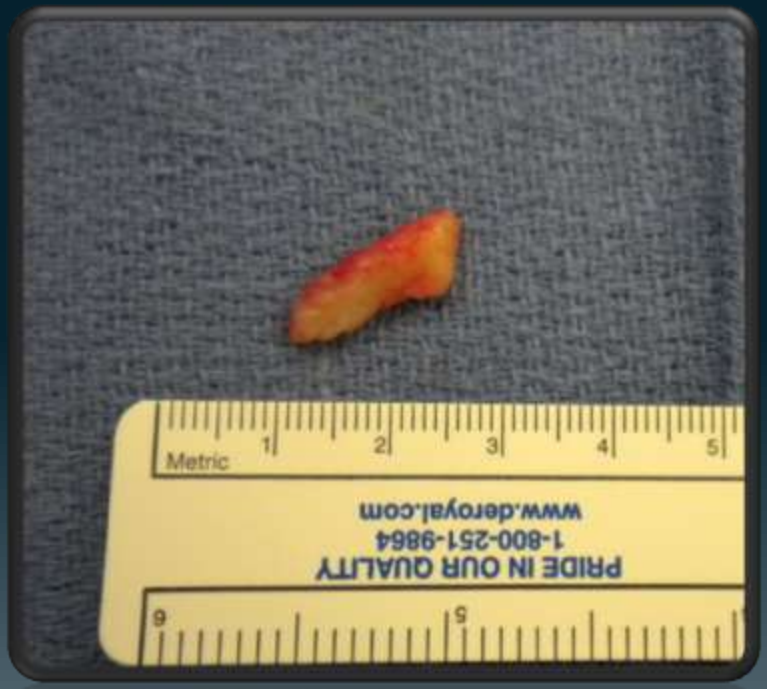


MEDICAL KNOWLEDGE, SYSTEMS-BASED PRACTICE

Hospital Course

- Pt underwent diagnostic biopsy of the right lacrimal gland.

- Pathology report: granulomatous inflammation, non-necrotizing type, with giant cells. No evidence of lymphoproliferative disease. Flow cytometry suboptimal due to low viability. Special fungal and AFB negative. **Findings favor sarcoid.**



PATIENT CARE, MEDICAL KNOWLEDGE

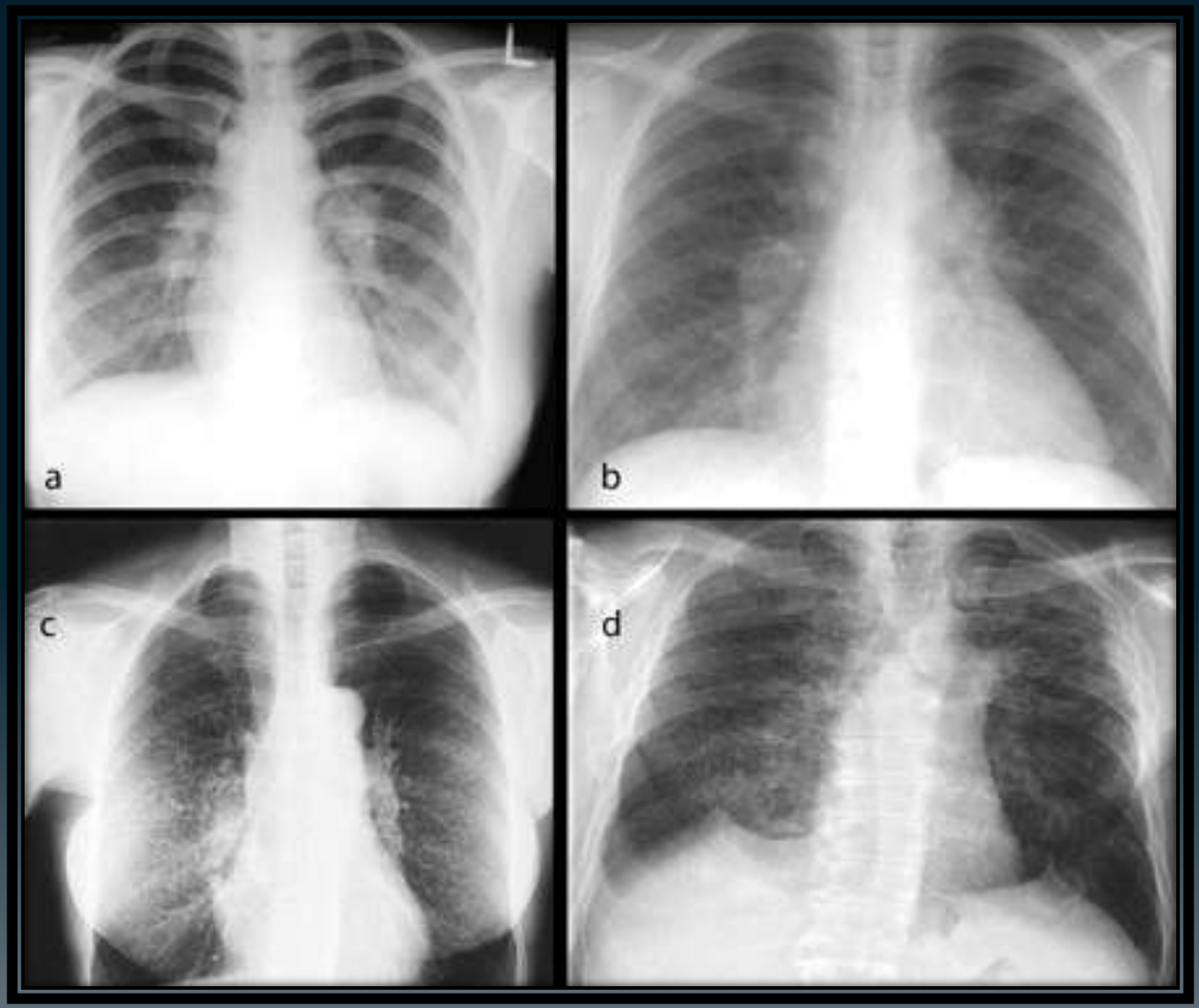
Sarcoidosis

- Multisystem granulomatous disorder – unknown etiology
  - Genetic predisposition assoc. w/ HLA-DRB1
- Worldwide: all races affected
- In the USA:
  - 10-20x more prevalent among African Americans compared to whites
  - Female >males
  - Younger patients (ages 20-50)
- With systemic sarcoidosis, 15-50% will have ocular involvement; most commonly manifests as uveitis

Systemic Manifestations

- Lungs (>90%)
  - Stage 1 (a) – Bilateral hilar lymphadenopathy (55-90%)
  - Stage 2 (b) – Pulmonary infiltrates w/BHL (40-70%)
  - Stage 3 (c) – PI alone (10-20%)
  - Stage 4 (d) – pulmonary fibrosis (0%)

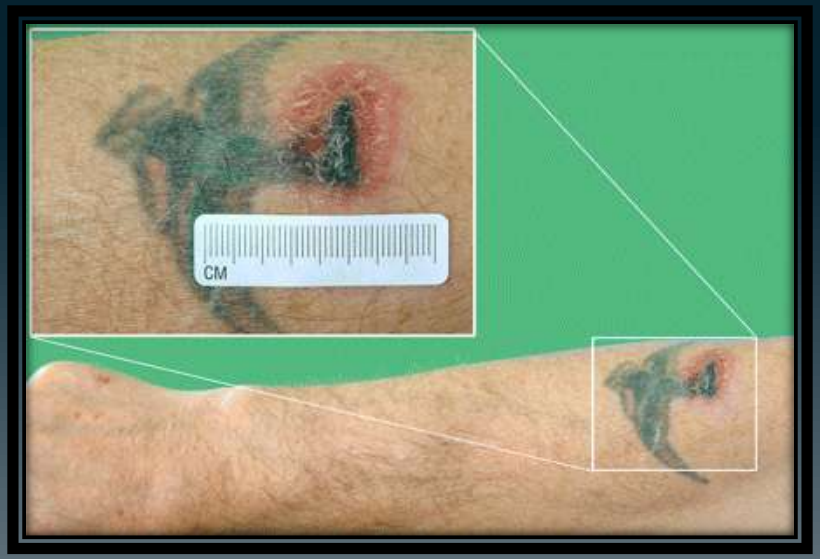
MEDICAL KNOWLEDGE

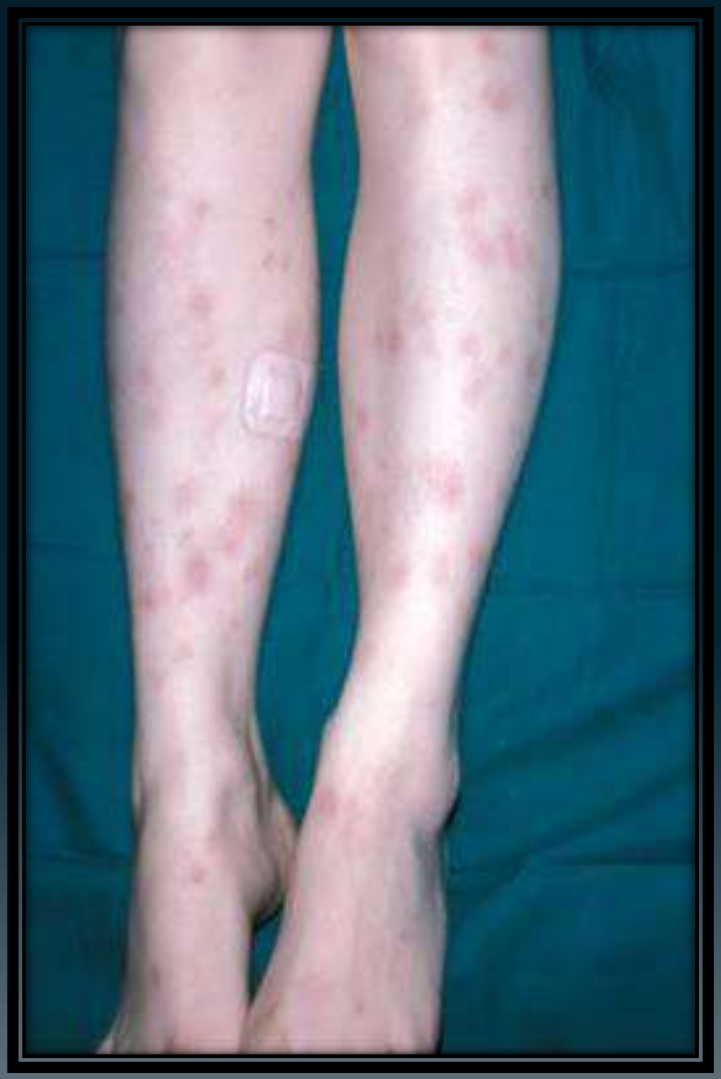


Images courtesy of Dempsey OJ, Paterson EW, Kerr KM, Denison AR. Clinical Review: Sarcoidosis. BMJ 2009; 339:b3206

Systemic Manifestations

- Skin (24%)-
  - Erythema nodosum
  - *Lofgren's syndrome* – EN, febrile arthropathy, systemic malaise, bilateral hilar lymphadenopathy, +/-acute iritis
    - >90% remission w/in 2 years





MEDICAL KNOWLEDGE

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Systemic Manifestations

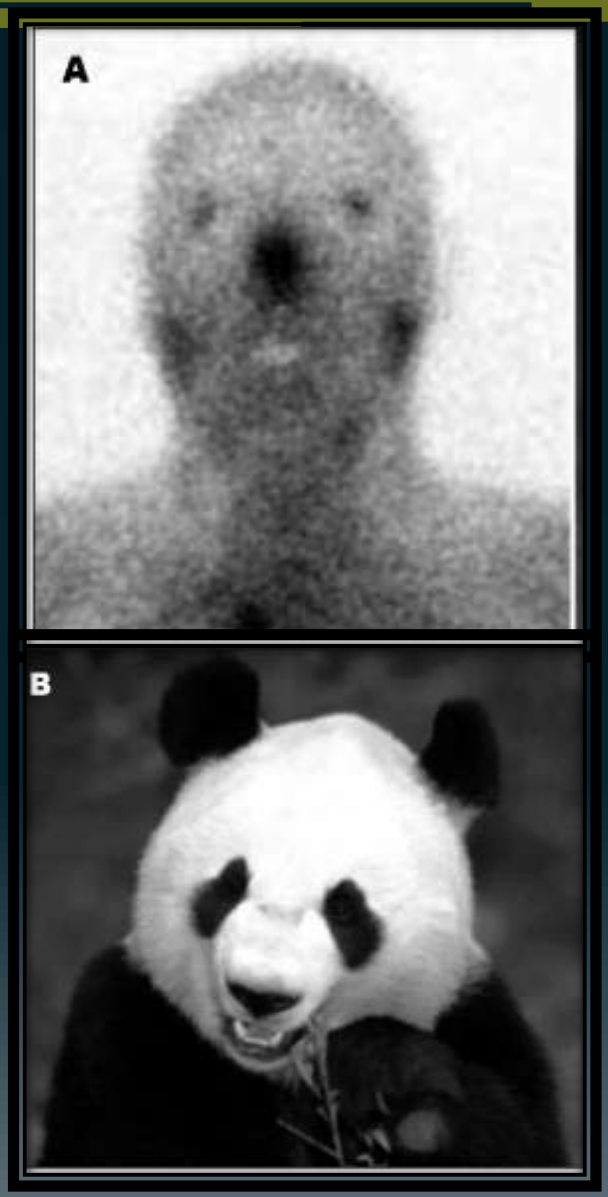
- Fatigue (66%)
- Lymphadenopathy (15%)
- Hepatic/GI (18%)
- Ocular (12%)
- Renal (5%)
- Neurological (5%)
  - Approx. 50% of these present with CN palsies, likely CNVII
- Cardiac (2-5%)
- Musculoskeletal (1%)

Pulmonary disease is the major cause of morbidity in USA.
Long term mortality rate for sarcoidosis: 5-8%
Cardiac disease most common cause of sarcoid-related death in Europe.

MEDICAL KNOWLEDGE

Heerfordt Syndrome

- aka uveoparotid fever
  - Present in approx 0.3% of patients with sarcoidosis
- Triad of:
  - **Uveitis**
  - **Parotitis**
    - Seen in 6% of sarcoid pts
  - **Fever**
  - **+/-Facial nerve palsy**



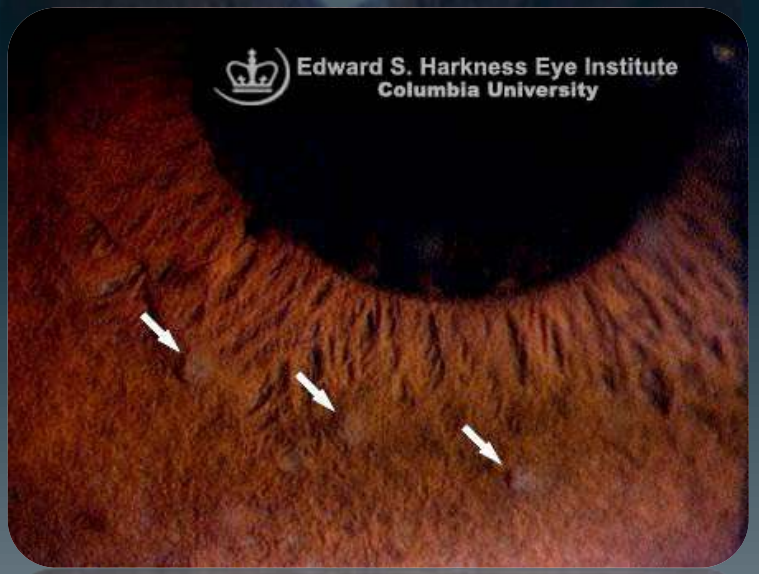
MEDICAL KNOWLEDGE

Images from source: Maranhao-Filho, Péricles and Vincent, Maurice B.. Neuropareidolia: diagnostic clues apropos of visual illusions. Arq. Neuro-Psiquiatr. 2009, vol.67, n.4, pp. 1117-1123

Sarcoid: Ocular Manifestations I

- Signs/symptoms: Periorbital skin lesions, Bussaca and Koeppe iris nodules, conjunctival granulomas, band keratopathy, lacrimal gland involvement ☐Sicca syndrome

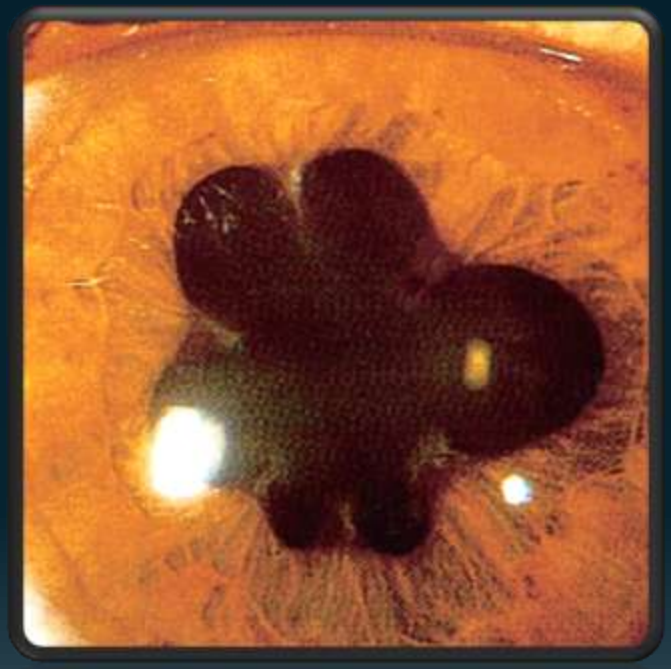
- Most common ocular presentation: anterior uveitis
  - Can present acutely or as chronic granulomatous iridocyclitis
  - Approx. 2/3 of pts with ocular sarcoidosis
  - Sarcoid accounts for ~3-10% of all cases of uveitis



MEDICAL KNOWLEDGE

Images from http://dro.hs.columbia.edu/irisnodules.htm

Sarcoid: Ocular Manifestations II - Anterior Uveitis



- Posterior synechiae
  - "Mickey mouse pupil"
- Mutton-fat keratic precipitates

Images from: Patel SJ,, Lundy D. Ocular Manifestations of Autoimmune Disease. Am Fam Physician. 2002 Sep 15;66(6):991-998, and www.rootatlas.com

Sarcoid: Posterior Uveitis

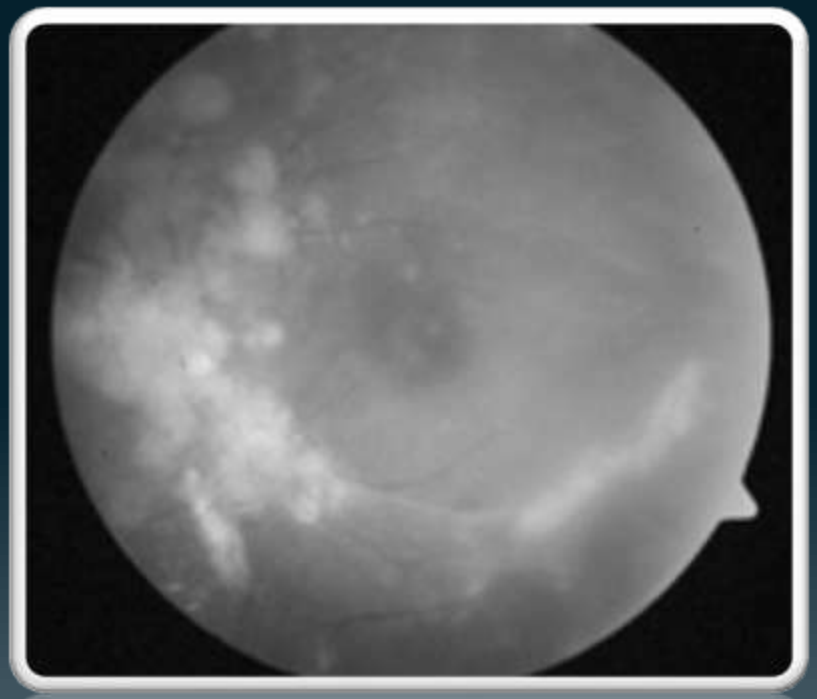


Image from www.informahealthcare.com

- May occur in up to 33% of sarcoid patients and is more visually disabling
- Non-specific findings:
  - "snowballs" in anterior vitreous
  - candle-wax drippings along retinal veins, perivenous sheathing
  - Choroidal granulomas
  - Dalen-Fuchs nodules
- Long-term sequelae: CME, cataract, glaucoma, hypotony, phthisis, subretinal neovascular membrane/net, NVD

MEDICAL KNOWLEDGE

Pathology

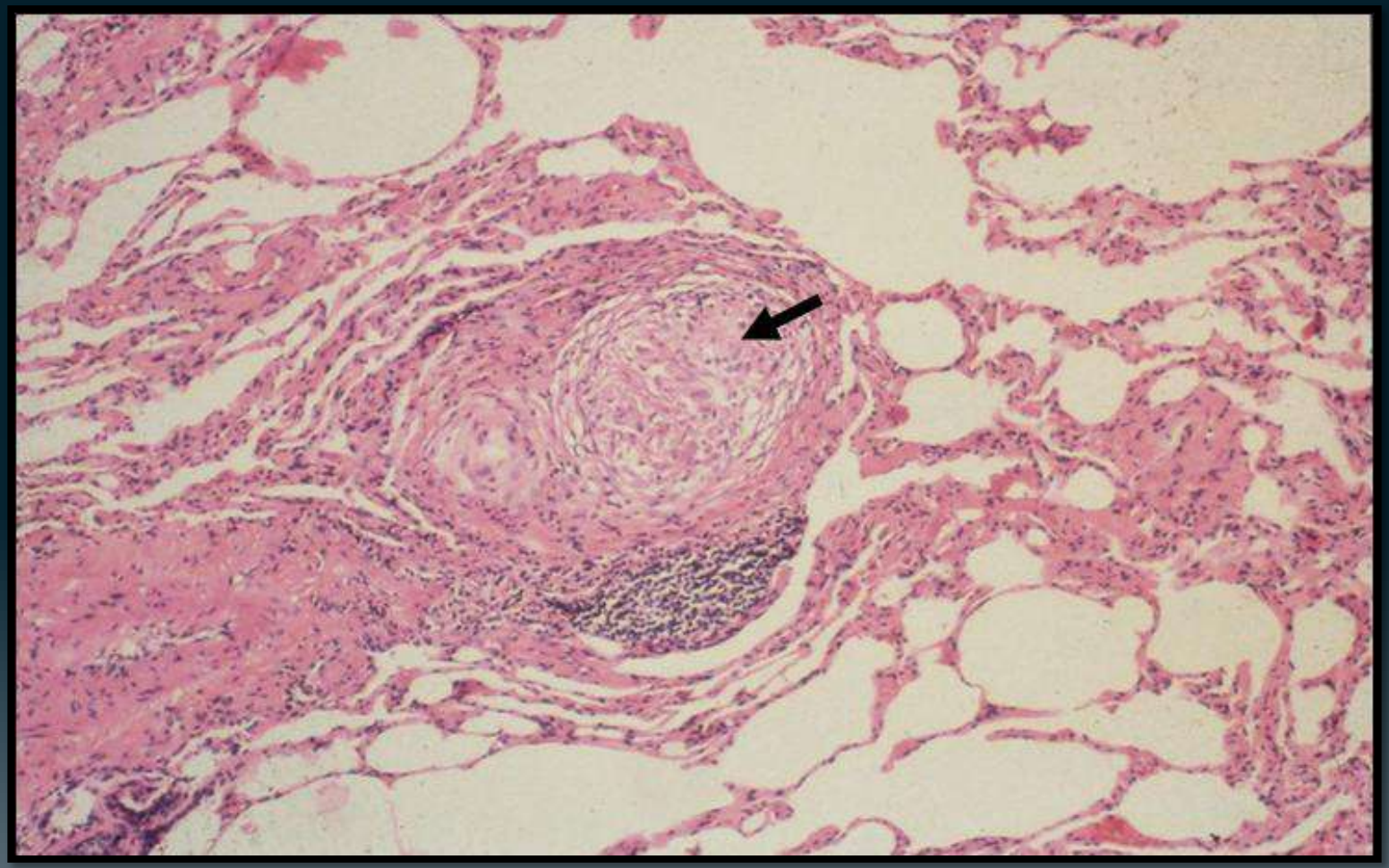


Image from source: Dempsey OJ, Paterson EW, Kerr KM, Denison AR. Clinical Review: Sarcoidosis. BMJ 2009; 339:b3206

MEDICAL KNOWLEDGE, PRACTICE-BASED LEARNING

Work-up

- History
  - Inquire about FHx? SHx? Travel? Sarcoid = dx of exclusion
- Physical exam
- Laboratory studies
  - CBC, ACE level, lysozyme, serum electrolytes (calcium), immunoglobulins, liver function studies, urine analysis/24 hr urine calcium, thyroid function tests
- Imaging studies
  - Chest X-ray, CT chest
- PPD/anergy panel
- EKG
- Tissue biopsy
- Pulmonary function tests

MEDICAL KNOWLEDGE, PRACTICE BASED LEARNING AND IMPROVEMENT

Treatment I

- **No treatment is warranted in asymptomatic cases**, and ~75% will have mild, stable disease that may be observed +/- spontaneous remission.
- Topical, periocular and systemic corticosteroids are the mainstay of therapy for sarcoidosis.
  - Approximately 25% of patients with sarcoidosis require treatment, including 10% of patients who have extrathoracic indications in critical organs (e.g., eye, brain, heart) and 15% of patients who have the indication of progressive pulmonary disease.
- The current corticosteroid protocol for systemic sarcoid disease is 40-80 mg prednisone daily for 8-12 weeks.
  - Gradual taper over a period of 6-12 months
- Maintenance therapy: for longer term tx, 10-15 mg of prednisone every other day

MEDICAL KNOWLEDGE, PRACTICE-BASED LEARNING AND IMPROVEMENT

Treatment II

- Anterior uveitis responds well to topical corticosteroids and cycloplegia.
  - Consider PO steroids for uveitis which includes optic nerve involvement; intermediate, posterior, or panuveitis; bilateral disease; and coexisting threshold systemic disease.

- Potency: PredForte 1% (prednisolone acetate) > generic prednisolone acetate >prednisolone phosphate
  - Loteprednol etabonate (Lotemax), may be effective second choice, with less chance of steroid-induced glaucoma
  - Weaker steroids, such as rimexolone (Vexol) and fluorometholone (FML), may play a role for patients in remission

MEDICAL KNOWLEDGE, PRACTICE-BASED LEARNING

Treatment III

- Intermediate and posterior uveitis ☐ responds well to depot corticosteroid injections. Topical corticosteroids and cycloplegics may supplement oral and/or sub-Tenon injections.
  - Injections may be repeated at weekly, biweekly, or monthly intervals, up to 3-4 times, before maximal benefit is reached.
- Orbital sarcoidosis ☐ usually requires oral corticosteroids, but retrobulbar injections of corticosteroids may be helpful.

<u>Corticosteroid-sparing agents:</u>

- **Cyclosporine A** – May be used in cases of steroid failures or intolerance; mixed results.
- **Methotrexate** and **Anti-tumor necrosis factor-alpha (TNF-alpha)** therapy (i.e., infliximab, etanercept, adalimumab) have been shown to be effective in recalcitrant uveitis.
- **Oral monoclonal antibody therapy** and **interferon therapy** investigation underway…

International criteria for the diagnosis of ocular sarcoidosis: results of the First International Workshop on Ocular Sarcoidosis (IWOS)

Herbort CP, Rao NA, Mochizuki M; Members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. Ocul Immunol Inflamm. 2009;17(3):160-169

- PURPOSE: To report criteria for the diagnosis of intraocular sarcoidosis, taking into account suggestive clinical signs and appropriate laboratory investigations and biopsy results.

- METHODS: An international group of uveitis specialists from Asia, Africa, Europe, and America met in a concensus conference in Shinagawa, Tokyo on October 28-29, 2006. Questionnaires sent re: clinical signs and laboratory investigations; those which received two-thirds majority of votes, were included in the list of signs consistent with ocular sarcoidosis. Diagnostic criteria were proposed based on ocular signs, laboratory investigations, and biopsy results.

PRACTICE-BASED LEARNING AND IMPROVEMENT

International criteria for the diagnosis of ocular sarcoidosis: results of the First International Workshop on Ocular Sarcoidosis (IWOS)

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Seven Signs on Intraocular Sarcoid

- (1) mutton-fat KPs/small granulomatous KPs and/or iris nodules (Koeppe/Busacca)
- (2) trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
- (3) vitreous opacities displaying snowballs/strings of pearls
- (4) multiple chorioretinal peripheral lesions (active and/or atrophic)
- (5) nodular and/or segmental peri-phlebitis (+/- candlewax drippings) and/or retinal macro aneurism in an inflamed eye
- (6) optic disc nodule(s)/ granuloma(s) and/or solitary choroidal nodule
- (7) bilaterality

Labs/Procedures

- (1) negative tuberculin skin test in a BCG-vaccinated patient or in a patient having had a positive tuberculin skin test previously
- (2) elevated ACE levels and/or elevated serum lysozyme
- (3) chest x-ray revealing bilateral hilar lymphadenopathy (BHL)
- (4) abnormal liver enzyme tests
- (5) chest CT scan in patients with a negative chest x-ray result

PRACTICE-BASED LEARNING AND IMPROVEMENT

International criteria for the diagnosis of ocular sarcoidosis: results of the First International Workshop on Ocular Sarcoidosis (IWOS)

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- Four levels of certainty for the diagnosis of ocular sarcoidosis (diagnostic criteria) were recommended in patients in whom other possible causes of uveitis had been excluded:
  - (1) biopsy-supported diagnosis with a compatible uveitis was labeled as **definite ocular sarcoidosis**
  - (2) if biopsy was not done but chest x-ray was positive showing BHL associated with a compatible uveitis, the condition was labeled as **presumed ocular sarcoidosis**
  - (3) if biopsy was not done and the chest x-ray did not show BHL but there were 3 of the above intraocular signs and 2 positive laboratory tests, the condition was labeled as **probable ocular sarcoidosis**
  - (4) if lung biopsy was done and the result was negative but at least 4 of the above signs and 2 positive laboratory investigations were present, the condition was labeled as **possible ocular sarcoidosis**.

- CONCLUSION: Various clinical signs, laboratory investigations, and biopsy results provided four diagnostic categories of sarcoid uveitis. This allows for prospective multinational clinical trials to be conducted using a standardized nomenclature, which serves as a platform for comparison of visual outcomes with various therapeutic modalities.

PRACTICE-BASED LEARNING AND IMPROVEMENT

Clinical features and diagnostic evaluation of biopsy-proven ocular sarcoidosis

Birnbaum, AD, Oh FS, Chakrabarti A, Tessler HH, Goldstein DA. Arch Ophthamol. 2011; 129(4) 409-413

- Purpose: To compare the clinical characteristics of uveitic sarcoidosis in African-American (AA) and non-AA patients with biopsy-proven sarcoidosis and to determine which diagnostic test results were most often suggestive of sarcoidosis in these patients.
- Methods: Retrospective chart review of patients with biopsy-proven sarcoidosis evaluated by the uveitis service between 1989 to 2009 at the U of Illinois, Chicago.
  - Exclusion criteria: positive PPD, FTA-ABS

PRACTICE-BASED LEARNING AND IMPROVEMENT

Clinical features and diagnostic evaluation of biopsy-proven ocular sarcoidosis (cont.)

Birnbaum, AD, Oh FS, Chakrabarti A, Tessler HH, Goldstein DA. Arch Ophthamol. 2011; 129(4) 409-413

- Results: Total 63 patients with biopsy-proven sarcoidosis amongst 3,912 adult patents with uveitis
  - Avg. age at presentation: 45 year (range: 20-84) no sex correlation
    - African American pts presented with ocular symptoms at an earlier age than non-AA pts (40 yrs vs 54 yrs)
  - African-American n=39 (62%) vs non-AA (38%): white n=19 (30%), Asian n=3 (4%), and Hispanic n=2 (3%)
  - 43 females (68%)

- Confirmation via biopsy: lungs n=34 (54%), LN n=10 (16%), skin n=7 (11%), conjunctiva n=4 (6%), vitreous n=2 (3%)
- Bilateral ocular involvement in 89% of cases
- AA patients more likely to present with granulomatous anterior involvement (72%) vs non-AA pts (25%)
- Positive family history in 5 patients

PRACTICE-BASED LEARNING AND IMPROVEMENT

Clinical features and diagnostic evaluation of biopsy-proven ocular sarcoidosis (cont.)

Birnbaum, AD, et al.

- Conclusions:
  - African American patients present at younger ages when compared to 2/3 of white patients that presented with sarcoid-related uveitis at >50 years of age.
  - Individual serums tests (ACE, lysozyme) have variable sensitivity and specificity and if used alone, will fail to identify many patients with true disease; therefore negative serum test results cannot exclude a clinical diagnosis of sarcoidosis.
  - Used in varying combinations, imaging studies along with serum markers identified 69 to 93% of patients with sarcoidosis.

PRACTICE-BASED LEARNING AND IMPROVEMENT

Patient Update

- The patient was started on oral corticosteroids with improvement in her symptoms. Diplopia resolved, now pain-free and states she feels “fantastic.”
- The patient is scheduled to have chest Xray today and pending labs studies as per PMD at Brooklyn Hospital.

PATIENT CARE, INTERPERSONAL SKILLS

Reflective Practice

- This patient presented with an interesting case of ocular sarcoidosis, with impressive findings of orbital involvement seen on imaging and with biopsy-confirmation of the diagnosis. Given the severity of symptoms, the patient was treated in a timely manner with oral corticosteroids with good response, while we await for further lab and imaging studies to determine the extent of her systemic disease.
- This case demonstrates the variability of the presentation of sarcoidosis, while the presentation highlights the importance of referral to a primary medical doctor (+/- pulmonologist, rheumatologist) for a comprehensive medical evaluation.

Core Competencies

- Patient Care: This patient was appropriately evaluated via physical exam and imaging, and subsequently received treatment as well as referral for further evaluation of systemic disease in a timely manner.
- Medical Knowledge: This presentation provides an overview of sarcoid, reviewing both its systemic and ophthalmic manifestations.
- Practice-Based Learning and Improvement: This presentation included information regarding the classification of ocular sarcoidosis, the evaluation and treatment of sarcoidosis.
- Interpersonal and Communication Skills: The patient was informed about possible etiologies for her symptoms and appropriately counseled about the risks/benefits/alternatives of lacrimal gland biopsy.
- Professionalism: We maintained good communication with the patient, informing her of results, and maintaining regular follow-up visits with ophthalmology.
- Systems-Based Practice: Appropriate care was provided via the services of radiology, pathology, the primary medical team and ophthalmology .

References

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Special thanks

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- SUNY Pathology Dept
- LICH Radiology Dept