07 – Syndromes that Masquerade as Infections

Speaker: Karen C Bloch, MD, MPH, FIDSA, FACP

2020 INFECTIOUS DISEASE BOARD REVIEW

Syndromes that Masquerade as Infections

Karen C. Bloch, MD, MPH, FIDSA, FACP
Associate Professor, Division of Infectious Diseases
Vanderbilt University Medical Center

*Special Thanks to Dr. Bennett Lorber!

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Mimics

- Many conditions masquerade as infections.
- Often with fever
- Sometimes focal abnormality
  - Cellulitis
  - Pneumonia
  - Lymphadenopathy
  - Splenomegaly

VS

2018 ID Board Content

Medical Content Category	% of exam
Bacterial Diseases	27%
HIV Infection	15%
Antimicrobial therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (non HIV)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care & Surgery	**18%**
Total	100%

Test taking tip

- Just as for infections, look for "buzz words" and "hooks"
- For infections:
  If I say "rabbit", you say…..

Test taking tip

- For infections:
  If I say "rabbit", you say…..

TULAREMIA

Test taking tip

I say ”Chitlins”

You say…..

Test taking tip

I say ”Chitlins”

You say…..

YERSINIA

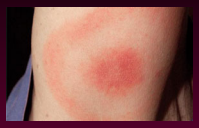
Test taking tip

I say ”Bull’s-eye rash”

You say…..

Test taking tip

I say ”Bull’s-eye rash”



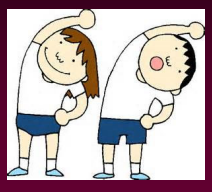
You say…..

Lyme disease
(or Erythema migrans or STARI)

My Approach to Mimics

- Think like an Internist.
- The key is recognition, not treatment.
- This talk will emphasize illustrative case
- Goal is to cover lots of non-infectious diseases rather than in-depth discussion

Quick Warm Up!



07 – Syndromes that Masquerade as Infections

Speaker: Karen C Bloch, MD, MPH, FIDSA, FACP

Question 1

A young man has oral and genital ulcers. You suspect Behçet's disease. Which of the following is most consistent with that diagnosis?

A. Evanescent, salmon-colored rash
B. High ferritin
C. Saddle nose deformity
D. Pustule at site of venipuncture
E. Posterior cervical adenopathy

Question 2

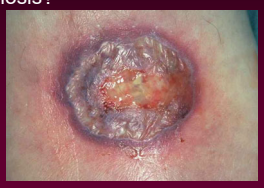
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

A. Ulcerative colitis
B. Adult onset Still's Disease
C. Acute leukemia
D. Systemic lupus
E. Ankylosing spondylitis

Question 3

A patient has a slowly enlarging ulcerated skin lesions on his shin after being hit by a soccer ball. Which of the following is the most likely diagnosis?

A. Pyoderma gangrenosum
B. Ecthyma gangrenosum
C. Erythema nodosum
D. Sweet Syndrome
E. Behçet's disease



Now on to our discussion, starting with a case.

Case 1

- 26yo man presents with a 1-month h/o fever, night sweats and fatigue. He was evaluated by his PCP with normal bloodwork and a positive monospot test. He was diagnosed with mononucleosis, but symptoms have persisted. He lives in Indiana with his wife and 2 yo son. They have 2 cats.

Case 1

- Exam:
  - Vitals:
    - T=38.4ºC, HR=118bpm
  - No lymphadenopathy
  - Palpable spleen tip
  - No rash
- Labs
  - CBC
    - WBC=2.7, plt=53
    - Normal H/H
  - Normal Cr
  - AST/ALT=38/200
  - Alk phos=494, bili=1.9
  - Ferritin=35,148 mg/ml

Question 4

- What is the most appropriate next study?
  - A. Flow cytometry of whole blood
  - B. ANA profile
  - C. EBV serologies
  - D. Soluble IL-2 receptor alpha level
  - E. Toxoplasma titer

Hemophagocytic Lymphohistiocytosis

- Immune activation syndrome
  - Primary: Familial due to genetic mutation
  - Secondary: Most commonly triggered by infections (EBV or other herpes group viruses, HIV, histoplasmosis, *Ehrlichia*, etc) or malignancy (lymphoma, leukemia)

HLH: Diagnostic Criteria

- Requires >=5/8
  - Fever
  - Splenomegaly
  - Cytopenias (any line)
  - Hypertriglyceridemia
  - Ferritin >500 mg/mL
  - Elevated soluble IL-2 receptor alpha (aka CD25)
  - Low NK cell activity
  - Hemophagocytosis on pathology

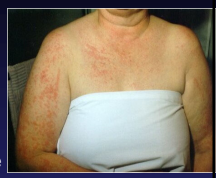
HLH Clues

- EBV or other infection with progressive symptoms
- Massively elevated ferritin
- Cytopenia with negative ID evaluation

Case 2

- A 39-year-old woman is seen on day 4 of hospitalization for high fever and leukocytosis. The fever had been present for 3 ½ weeks and was accompanied by severe arthralgias of the knees, wrists and ankles as well as myalgias. A severe sore throat was present during the first week of the illness.

- Exam: T=104.2º F.
- Tonsilar swelling and erythema is present, with tender cervical LN.
- Spleen tip is palpable.
- The R wrist is swollen and painful.
- A rash present on the trunk and extremities, most prominently under the breasts and in the area of her underwear waistband.



Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

Major:	Minor:
1. Fever >39ºC for ≥1week	1. Sore throat
2. Arthritis/arthralgia >2 wks	2. Lymphadenopathy
3. Typical rash (during febrile episodes)	3. Lg Liver or spleen
4. Leukocytosis ≥10K with >80% PMNs.	4. Abnl LFTs
	5. Negative ANA & RF

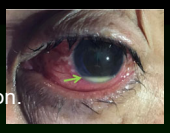
Adult Still's

- Buzz words and associations:
  evanescent, **salmon-colored** rash

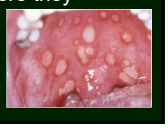
- Other clues:
  - Multi-system illness
  - Elevated ferritin
  - Pharyngitis
  - Koebner phenomenon = rash elicited by stroking skin or areas of pressure.

Case 3

- A 24-year-old man is referred from the ED for ulcers of the mouth and penis. Three months ago he came to the U.S. from Japan to attend graduate school.
- He has a history of intermittent, painful oral ulcers for 3-4 years. Four days ago he developed a painful ulcer on the penile shaft. He recalls a similar lesion 2 months earlier. He takes no medicines and denies sexual contact for the past 5 years.



- Exam: afebrile.
- Left eye is inflamed and there is a hypopyon. Numerous ulcers on the oral mucosa.
- There is a 0.5cm ulcer on the penis.
- A 6mm papulo-pustular lesion is present in the right antecubital fossa; the patient says that is where they drew blood yesterday in the ED.



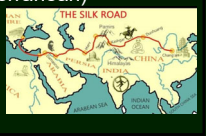
- Labs: Hb 12.1; WBC 13,750. HIV negative

Question 6

- The most likely diagnosis is?
  - A. Syphilis
  - B. Behçet's disease
  - C. Herpes simplex virus infection
  - D. Sarcoidosis
  - E. Cytomegalovirus infection

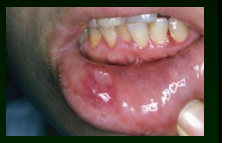
Behçet's disease

- Pleomorphic vasculitis with clinical diagnosis
  Recurrent oral ulcers (≥3 per year) PLUS 2 of the following
  - recurrent genital ulcers
  - eye (uveitis, retinitis, hypopion) or skin lesions (EN, papules)
  - pathergy (red papule developing 24-48 hrs after needlestick)
- Think "silk road" ancestry (Asia->Mediterranean)
- Less common manifestations
  - GI disease (abdo. Pain, bloody diarrhea)
  - CNS disease (aseptic meningitis)
  - Arterial and venous thrombosis
- Treatment: colchicine



Behçet's disease

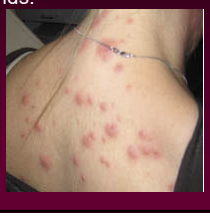
- Buzz words and associations:
  - Mucosal ulcers on mouth and/or genitals PLUS….
    - GI symptoms (vs CMV)
    - Aseptic meningitis (vs HSV)
    - Visual changes
    - Pathergy (needle or IV site)
  - Asian or Mediterranean ancestry



Case 4

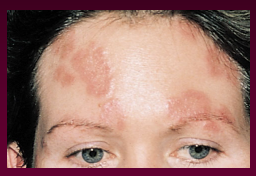
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever. Following marrow recovery, she was d/c to home. The day of admit she developed fever without localizing symptoms. CBC showed a white blood cell count of 12,250 with 20% bands.
- Exam: T 101.4; P 98; otherwise unremarkable.
- Blood cultures were sent, and she was admitted and started on broad spectrum empiric antibiotics.

- HD 2: Fever persists, with interval development of raised, red-purple, tender, non-pruritic papules and nodules on her face, neck and the dorsum of her hands.



HD 3: Fever persists; some of the papules develop a plaque-like appearance

HD 4: biopsy: dense dermal perivascular infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative.



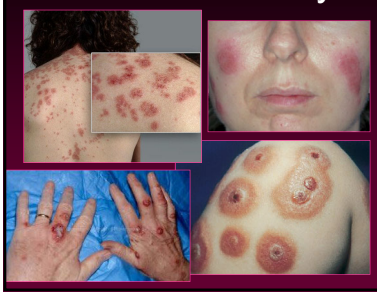
Question 7

- Which of the following is the most likely diagnosis?
  - A. Ecthyma gangrenosum
  - B. Pyoderma gangrenosum
  - C. DRESS
  - D. Leukemic infiltrates
  - E. Sweet syndrome

Sweet Syndrome

- AKA acute febrile neutrophilic dermatosis
- Three variants:
  - Idiopathic or "classical"->50% (IBD, post viral illness, preg, etc)
  - Malignancy associated~20% (may precede dx, AML most frequent)
  - Drug induced-G-CSF most common, usually 2 wk after exposure
- Fever universally present
- Rarely oral ulcers or extra-cutaneous disease characterized by neutrophilic infiltrate on path
- Labs notable for leukocytosis with left shift, inc ESR & CRP
- Path diagnostic—Neutrophilic infiltrate without vasculitis

Sweet Syndrome



- Lesions appear **abruptly** and usually **tender**.
- May be single or multiple, often involving **dorsum of hand**.
- Red, violaceous, or yellow center
- Nodular or **plaque-like**
- Central umbilification with **target appearance**

Sweet Syndrome

- Buzz words and associations:
  - Acute
  - Febrile
  - Neutrophilic (peripheral and on path)
  - Dermatosis

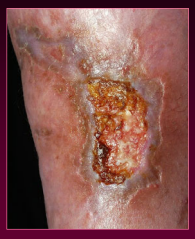
Be suspicious in patients with malignancy (esp AML, past or present), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 5

- A 33-year-old recent immigrant from Central America is seen for a chronic ulcer of the leg.
- The ulcer has progressively enlarged over 3 months. after he bumped his leg on a table. Several courses of oral antibiotics have been given with no response.
- For the past year he has been troubled by an "upset stomach" = intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool. He has also had intermittent fever, sometimes accompanying diarrhea, sometimes not.

- Exam:
  - T 100.2; skin lesion on leg (see image)
  - Slight, diffuse abdominal tenderness.
  - Otherwise unremarkable.
- Labs:
  - Hb 12.4; WBC 11,150, ESR=79, CRP=110
  - UA normal
  - Basic metabolic panel normal
  - Chest x-ray normal

Leg lesion



Painful and irregularly shaped ulcer with undermined borders

Question 8

Which one of the following is the most likely diagnosis?

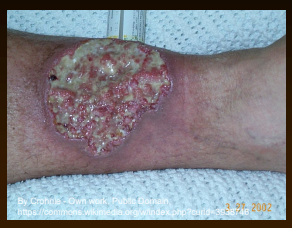
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Necrotizing fasciitis
E. Squamous cell cancer

Pyoderma gangrenosum

- *Another* neutrophilic dermatosis
  - Indolent, fever rare (vs Sweet)
- Papule at site of often trivial trauma, progressing to a **painful** ulcer with violaceous or red border and necrotic base
- >50% of cases occur with systemic illnesses (but may precede dx, or occur independent of flares)
  - IBD (MOST COMMON COMORBIDITY; UC>Crohn's)
  - Inflammatory arthritis
  - Solid organ or heme malignancy

Pyoderma Gangrenosum

- Buzzwords & Hooks
  - Minor trauma (Pathergy) frequent
  - Painful, progressive **undermined ulcer** with violaceous edges and **necrotic base**
  - Concomitant IBD, arthritis, neoplasm



Case 6

A 79-year-old woman is seen for 3 weeks of fever and fatigue. Except for hypertension, she has no medical problems. Has noted jaw discomfort when chewing food, and 1 week ago had a brief episode of double vision. One week before she became ill she attended a wedding at which she ate pork from a whole pig that was roasted on a spit over an open fire.

Question 9

Which of the following is most likely to yield a diagnosis?

A. Anti-neutrophil cytoplasmic antibody (ANCA)
B. *Taenia solium* serology
C. Blood cultures
D. Arteriography
E. Temporal artery biopsy

Giant Cell Arteritis

- GCA (AKA temporal arteritis)= pan-arteritis of extracranial branches of the carotid.
- A disease of the older adult: Almost all >50years
- Clinical findings: Fever, HA, scalp or TA tenderness, jaw claudication, amaurosis fugax
- Marked inc ESR/CRP suggestive, TA biopsy diagnostic
- Immediate steroid therapy indicated if visual changes to prevent blindness (won't affect biopsy yield for up to two weeks).

Giant Cell Arteritis

Buzz words and associations:

Age >50 years; fever (FUO) and:

scalp or TA tenderness

diplopia or transient visual loss

jaw or tongue fatigue or pain while chewing

high sedimentation rate

07 – Syndromes that Masquerade as Infections

Speaker: Karen C Bloch, MD, MPH, FIDSA, FACP

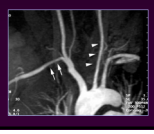
Polymyalgia Rheumatica (PMR)

Buzz words and associations:

- Half of all patients with polymyalgia rheumatic (PMR) have concomitant GCA
- Fever not prominent (may be low grade) in absence of GCA
- Aching and **morning stiffness** in proximal muscles of shoulder and hip girdle
- Gel phenomenon

Takayasu Arteritis

- Another large vessel vasculitis involving aorta, branches and pulmonary arteries.
- Buzz words and associations:
  - Young woman (>80%), Asian ancestry
  - Subacute onset of fever, weight loss, arthralgias and myalgias
  - Carotidynia (pain with palpation), decreased pulses
  - Extremity claudication; visual changes; TIAs
- Dx: Arteriography



Case 7

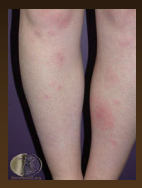
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness. She notes subjective chills and sweats.
- She does recall several tick bites over the last 2 months

Exam:

T 101.2; Pulse 72; BP 110/70

Bilateral synovial thickening of ankles with warmth and tenderness to passive movement

Skin exam with painful pre-tibial nodules



Labs:

WBC 8.8 (76% segs)

CRP=167

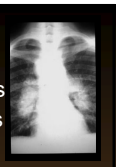
Uric acid=4.4, RF <15, CCP negative

Question 10

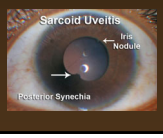
Which of the following is most likely to be diagnostic?

A. Chest x-ray
B. Serology for *Borrelia burgdorferi*
C. Urine *Histoplasma* antigen
D. Arthrocentesis
E. Skin biopsy

Sarcoidosis

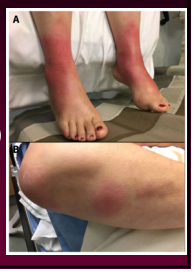


- A common mimicker with protean presentations
- Extra-pulmonary presentations in ~1/3 of cases
- Lofgren Syndrome
  - Clinical diagnosis: Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, parotid enlargement, uveitis
  - Aseptic meningitis with basilar enhancement
  - Non-caseating granulomas



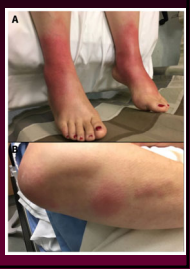
Erythema nodosum

- NO cause >50% of cases
- Drugs: sulfonamides, Penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechet's)
- Microbes:
  - EBV, Hep B/C
  - *Streptocci*, *Bartonella,* TB
  - Endemic fungi



Erythema nodosum

- NO cause >50% of cases
- Drugs: sulfonamides, Penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechet's)
- Microbes:
  - EBV, Hep B/C
  - *Streptocci*, *Bartonella,* TB
  - Endemic fungi



Case 8

- A 19-year-old recent immigrant from Iraq is hospitalized for 2 day history of fever and severe abdominal pain
- He says he has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the removed appendix was normal. Other episodes resolved spontaneously after 2-3 days.

- Exam:
  T 102.2; pulse 114; no rash
  Abdominal guarding, rebound tenderness, hypoactive bowel sounds.
- Labs:
  Hb 12.4; WBC 16,650; UA normal
  Basic metabolic panel normal
  no occult blood in stool
  CT of abdomen and pelvis normal

Question 11

The most likely diagnosis is:

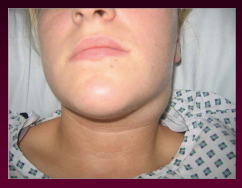
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

- Hereditary auto-inflammatory disease
- Sporadic, recurrent attacks of fever & serositis (peritonitis, pleuritis, arthritis) manifesting as pain.
- Dx: Genetic testing
- Buzz words and associations:
  - Periodic episodes (fever PLUS…)
  - Colchicine responsive illness
  - Mediterranean ethnicitiy

Case 9

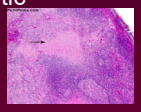
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



- Exam:
  T 101.4; unilateral anterior and posterior cervical enlarged lymph nodes, firm, and mildly tender. Otherwise unremarkable.
- Labs:
  Hb 13.9; WBC 4,900 (9% atypical lymphocytes)
  Basic metabolic panel normal
  Chest x-ray normal
  ESR=72
  Monospot: Negative

- Serologic studies:
  EBV consistent with prior infection
  CMV, *Toxoplasma*, *Bartonella* titers negative
  RF, ANA, ds-DNA negative
- Lymph node pathology:
  necrotizing lymphadenitis with histiocytic infiltrate and phagocytosed debris.

  Stains for AFB and fungi negative.



Question 12

Which one of the following is the most likely diagnosis?

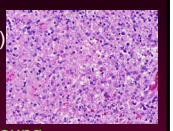
A. Cat Scratch Disease
B. Adult Still's Disease
C. Sarcoidosis
D. Kikuchi Disease
E. Non-Hodgkin Lymphoma

Kikuchi Disease

- AKA acute necrotizing histiocytic lymphadenitis
- Self-limited condition of unknown cause
- Typically young women
- No racial or ethnic proclivity (more common in Asia)
- fever & cervical LAN (esp posterior, usually unilateral).
- May also see morbiliform exantham, rarely extra cervical LAN, aseptic meningitis, uveitis.
- Variably leukopenic and atypical lymphocytes (25% of cases).

Kikuchi's Disease

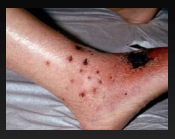
- Diagnosis by lymph node biopsy:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

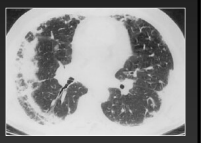


Case 10

- A 41-year-old woman is seen for fever, worsening respiratory symptoms, and a rash.
- She has long-standing asthma with frequent exacerbations
- She uses an inhaler several times a day and was recently placed on a leukotriene receptor antagonist. She is being tapered off steroids which she has taken for several months.

- Exam: Temp 101.5; RR 24
- Diffuse wheezing; palpable purpura with nodules on elbows and legs.
- Labs: WBC 15,230 (22% eosinophils).
- CT scan: bilateral peripheral infiltrates.
- Skin nodule biopsy: granulomas





Question 13

Which one of the following is the most likely diagnosis?

A. Strongyloidiasis
B. Disseminated histoplasmosis
C. Sarcoidosis
D. Allergic bronchopulmonary aspergillosis
E. Churg-Strauss syndrome

Churg-Strauss Syndrome

- AKA eosinophilic granulomatosis with polyangiitis (EGPA)
- Multisystem, small vessel vasculitis with allergic rhinitis, asthma, peripheral and lung eosinophilia.
- Most often involves lung and skin, but can involve heart, GI tract, and nervous system.
- Presence of blood eosinophilia and peripheral pulmonary infiltrates in setting of difficult to control asthma
- Tapering of steroids often "unmasks" EGPA
- May be p-ANCA positive.

Churg-Strauss Syndrome

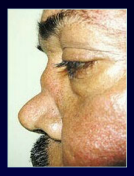
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 11

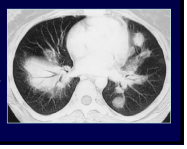
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati, OH on business.
- He has no pets and takes only an OTC decongestant

Exam:
- T 100.2; RR 18;

Nasal deformity with perforation of septum
Lungs clear; rest of exam normal.



- Labs:
  WBC 6,900 with normal differential;
  UA 30-50 RBC; BMP normal
  Chest CT: bilateral nodules with cavitation.



Question 14

- The diagnosis will most likely be supported by which one of the following?
  - A. c-ANCA
  - B. Anti-glomerular basement membrane Ab
  - C. Histoplasma urine antigen
  - D. Angiotensin converting enzyme (ACE)
  - E. Pulmonary angiogram

Granulomatosis with polyangiitis (GPA) (formerly Wegener's)

- Systemic vasculitis of medium and small arteries.
- Primarily involves the upper and lower respiratory tracts and kidneys (Pulmonary-Renal Syndrome).
- Limited to upper respiratory tract or lungs in 25% (most often young women).
- Variably involves joints, eyes, skin, and nervous system.

Granulomatosis with polyangiitis

- Dx:
  Suggestive: Pos ANCA (~85%)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

Buzz words and associations:
Nasal symptoms (Saddle nose and perforation)
CT nodules
Respiratory and renal findings (hematuria)

Case 12

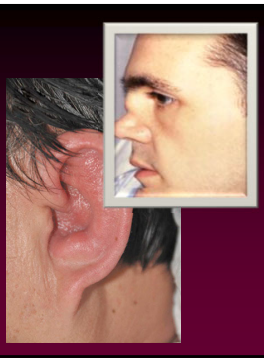
- A 42-year-old man is seen for his third episode of cellulitis of the external ear.
- Two previous episodes involving the same ear, 2 and 5 months ago, responded very slowly to antibiotics.
- He has a several year history of chronic nasal stuffiness and had an episode of knee arthritis in the past year but is otherwise well.

Case 12

Exam:
Afebrile
Left auricle is inflamed and tender, ear lobe is spared.

He has a saddle-nose deformity; the nasal mucosa is normal.

Labs: normal



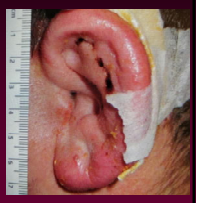
Question 15

The most likely diagnosis is?

A. Invasive external otitis
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

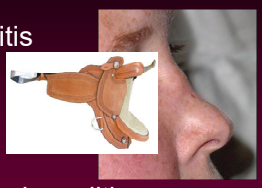
Relapsing Polychondritis

--Immune-mediated condition.
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.
--Clinical diagnosis.



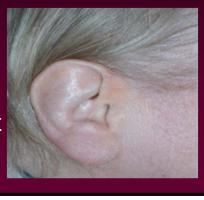
Saddle-nose Deformity

Relapsing polychondritis
Lepromatous leprosy
Congenital syphilis
Leishmaniasis
Granulomatosis with polyangiitis
Cocaine use



Relapsing Polychondritis

- Buzz words and associations:
  - Recurrent "cellulitis" (cartilage inflammation)
  - Saddle-nose
  - Cauliflower ear
  - Sparing of ear lobe
  - Parasternal joint involvement



That's all!

Karen.bloch@vumc.org