

Syndromes that Masquerade as Infections

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1



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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2

ID Board Content	
<u>Medical Content Category</u>	<u>% of exam</u>
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%

3

Mimics

- Many conditions masquerade as infections
 - Fever almost universally present
 - Sometimes focal abnormality
 - Cellulitis vs stasis dermatitis
 - Viral vs Organizing Pneumonia
 - Lymphadenitis vs Lymphoma



VS

4

Test Taking Tip

- Just as for infections, look for “buzzwords” and “hooks”
- For infections:
 - If I say, “skinned rabbit”, you say.....

5

Test Taking Tip

- For infections:
 - If I say, “rabbit”, you say.....



(Pulmonary) TULAREMIA

6

Test Taking Tip

If I say, “chitterlings” (aka chitlins, aka hog intestines)

You say.....



7

Test Taking Tip

If I say, “chitterlings”

You say.....



YERSINIA (gastroenteritis)

8

Test Taking Tip

If I say, "Bull's-eye rash"

You say.....



9

Test Taking Tip

If I say, "Bull's-eye rash"

You say.....



Lyme disease
(or **Erythema migrans** or **STARI**)

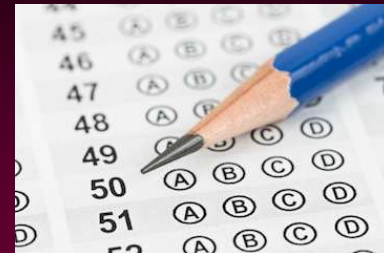
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My Approach to Mimics

- Think like an Internist
- The key is recognition, not treatment
- This talk will emphasize illustrative cases
- Goal is to cover lots of non-infectious diseases rather than in-depth discussion using **buzzwords** for easy recognition!

11

Examples



12

41 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

13

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

14

Question #3

A patient has a slowly enlarging ulcerated skin lesion on his shin after being hit by a soccer ball.

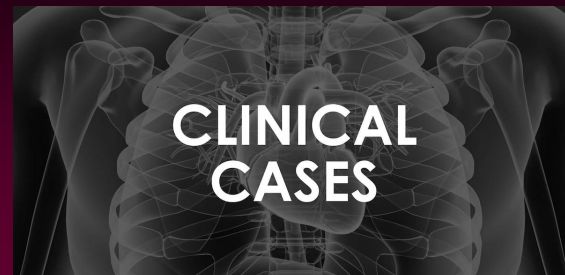
Which of the following is the most likely diagnosis?

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



15

But this being boards...



To optimize learning: **CLOSE THE SYLLABUS**

16

41 Syndromes that Masquerade as Infections

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Question #4

- 26-year-old man presents with a 1-month h/o fever, night sweats and fatigue. He was evaluated by his PCP 2 weeks ago with a positive monospot.
- Fevers have persisted, and he has lost 10 lbs since the positive test.
- He lives in Indiana with his wife and 2 yo son, who are healthy. They have 2 cats.

17

Question #4

- Exam:
 - Vitals:
 - T=**38.4°C**, HR=118 bpm
 - No lymphadenopathy
 - **Palpable spleen tip**
 - No rash
- Labs
 - CBC
 - WBC=**2.7**, plt=**53**
 - Normal H/H
 - Normal Cr
 - AST/ALT=**120/200**
 - Alk phos=**494**, bili=**1.9**
 - Ferritin=**35,148** mg/ml

18

Question #4

What is the most appropriate next study?

- A. Flow cytometry of whole blood
- B. ANA profile
- C. CMV PCR
- D. Soluble IL-2 receptor level
- E. Toxoplasma titer

19

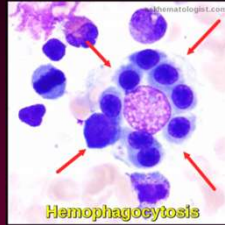
Hemophagocytic Lymphohistiocytosis

- AKA HLH
- Immune activation syndrome
 - Primary (Peds): Familial due to genetic mutation
 - Secondary (Adult or peds):
 - Infections (**EBV** or other herpes group viruses, HIV, histoplasmosis, *Ehrlichia*, COVID-19 etc.)
 - Malignancy (lymphoma, leukemia)

20

HLH-2024: Diagnostic Criteria

- At least **5/7** of the following:
 - Fever ($T > 38.5^{\circ}\text{C}$)
 - Splenomegaly
 - Cytopenias (2/3 lineages)
 - Hypertriglyceridemia ($> 3\text{mmol/L}$)
 - **Ferritin** $> 500\text{ mcg/mL}$
 - Elevated soluble IL-2 receptor (aka sCD25)



Note: NK cell function now a functional criteria

HLH Clues

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

21

22

Question #5

- A 39-year-old woman is admitted for fever of 3 weeks associated with diffuse arthralgias involving the knees, wrists and ankles.
- A severe sore throat was present during the first week of the illness but has resolved.

23

Question #5

Physical Exam

- $T = 104.2^{\circ}\text{F}$
- Tender cervical LAN appreciated
- Spleen tip is palpable
- Both knees are swollen & painful
- A rash is present on the trunk and extremities, most prominently under the breasts and in the area of her underwear waistband



24

Question #5

- Labs:
 - Ferritin **3600** ng/ml (nl 40-200)
 - WBC **32,200** (89% neutrophils)
 - **AST and ALT 3x** normal
 - **ESR and CRP 5x** normal
 - ANA and RF negative
 - Throat and blood cultures are so far negative
- On afternoon rounds with the attending, the fever has resolved with Tylenol and the rash is no longer present

25

Question #5

What is the most likely diagnosis?

- A. Lymphoma
- B. Adult Still's Disease
- C. Acute Rheumatic Fever
- D. Cryoglobulinemia
- E. Kikuchi Disease

26

Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

Major:

1. Fever $>39^{\circ}\text{C}$ for ≥ 1 week
2. Arthritis/arthralgia >2 wks
3. Typical rash (**during febrile episodes**)
4. Leukocytosis $\geq 10\text{K}$ with $>80\%$ PMNs

Minor:

1. Sore throat
2. Lymphadenopathy
3. Lg Liver or spleen
4. Abnl LFTs
5. Negative ANA & RF

27

Adult Still's Disease

- Buzzwords and associations:

Evanescant, salmon-colored rash



=



Koebner phenomenon (rash at pressure sites)

28

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Question #6

- A 24-year-old man was referred by the ED for evaluation of ulcers of the mouth and penis. He was born in Japan and is in the U.S. to attend graduate school.
- He has a history of recurrent painful oral ulcers for 3-4 years. Four days ago, he developed a painful ulcer on the penile shaft. He takes no medicines and denies sexual contact for the past 5 years.

29

Question #6

- Left eye is inflamed and there is a hypopyon
- Numerous painful 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 where they drew blood yesterday in the ED



30

Question #6

What is the most likely diagnosis?

- A. Syphilis
- B. Behçet's disease
- C. Herpes simplex virus infection
- D. Sarcoidosis
- E. Cytomegalovirus infection

31

Behçet's Disease



Pleomorphic vasculitis diagnosed clinically

- Recurrent **oral ulcers** (≥ 3 per year) PLUS 2 of the following
 1. Recurrent **genital ulcers**
 2. **Eye** (uveitis, retinitis, hypopyon)
 3. Skin lesions, esp **pathergy** (red papule 24-48 hours after needlestick)
- Less common manifestations (oral ulcers PLUS...)
 - GI disease (abdominal pain, bloody diarrhea)
 - Aseptic meningitis
 - Arterial and venous thrombosis

32

Behçet's Disease



VS



- **Ulcers** is the buzzword, but the trick is differentiation from infectious causes (HSV, coxsackie, etc.)



- Additional Clues

Recurrence

Ocular findings

Pathergy (needle or IV site)

33

Question #7

- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever that resolved with marrow recovery
- She presents with a 1-day history of fever without localizing symptoms
- Exam: T 101.4°F; P 98; otherwise, unremarkable
- CBC showed a white blood cell count of 12,250 with 20% bands

34

Question #7

Hospital Day 2:

- Fever persists despite broad spectrum antibiotics
- Interval development of raised, red-purple, tender papules and nodules on her face, neck and the dorsum of her hands



35

Question #7

Hospital Day 3:

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

Hospital Day 4:

- Skin biopsy with dense perivascular infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative



36

Question #7

Which is the most likely diagnosis?

- A. Ecthyma gangrenosum
- B. Pyoderma gangrenosum
- C. DRESS
- D. Leukemic infiltrates
- E. Sweet syndrome

37

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, antibiotics
- **Fever and Rash** universally present
- Rarely oral ulcers or extra-cutaneous disease characterized by neutrophilic infiltrate on path
- Lab tests with leukocytosis with left shift, inc ESR & CRP
- Path diagnostic – **Neutrophilic infiltrate without vasculitis**

38

Skin Lesions in Sweet Syndrome

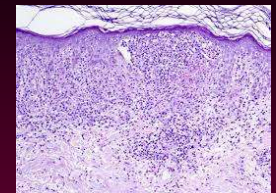


- Lesions appear **abruptly** and usually **tender**
- May be single or multiple, often involving **dorsum of hand**
- Red, violaceous, or yellow center
- Nodular or **plaque-like**
- Central umbilication with **target appearance**

39

Sweet Syndrome

- Buzzwords and associations:
 - Fever and a rash
 - Neutrophilia (peripheral and on **path**)
- Be suspicious in patients with malignancy (esp **AML**), **IBD**, recent **URI**, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks



40

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Question #8

- A 33-year-old recent immigrant from Central America is seen for a leg ulcer
- The ulcer has progressively enlarged over 3 months after he bumped his leg on a table
- There has been no response to oral antibiotics.
- For the past year he has been troubled by an “upset stomach”. On further probing, he describe intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool

41

Question #8

- Exam:
 - T 100.2°F
 - Abdo pain to palpation
 - Skin lesion
- Labs:
 - WBC 11,150 (2% eos)
 - ESR=79, CRP=110
 - BMP normal
 - Chest x-ray normal



42

Question #8

Which one of the following is the most likely diagnosis?

- A. Ulcerative colitis
- B. Cutaneous leishmaniasis
- C. Amebic colitis
- D. Cutaneous blastomycosis
- E. Squamous cell cancer

43

Pyoderma gangrenosum

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

44

Pyoderma gangrenosum

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



45

Question #9

- A 79-year-old woman is seen for 3 weeks of fever and fatigue
- One week earlier she developed jaw discomfort when chewing food and had a brief episode of double vision
- One month ago, she attended a luau and ate roast suckling pork prepared over an open fire



46

Question #9

- Exam:
 - T 102.2°F, P 104, BP 124/84
 - Slight tenderness over left scalp
 - Mitral regurgitant murmur
 - Rest of exam normal
- Labs:
 - Hb 9.8; WBC 9800, normal diff
 - UA normal
 - Basic metabolic panel normal
 - Sedimentation rate 147

47

Question #9

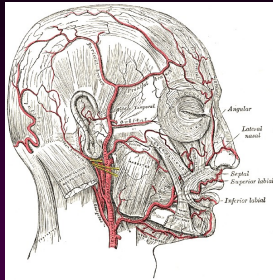
Which of the following is most likely to be diagnostic?

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

48

Giant Cell Arteritis

- Extracranial branches of the carotid
- Clinical findings:
 - Fever (almost exclusively older adults)
 - Scalp or TA tenderness, jaw claudication
 - Amaurosis fugax or sudden vision loss
- Marked inc ESR/CRP suggestive, TA biopsy diagnostic
- Immediate steroid therapy indicated if visual changes to prevent blindness



49

Giant Cell Arteritis

Buzzwords & Associations:

FUO in a patient **>50** years **PLUS**

- Scalp or TA tenderness
- Visual symptoms (diplopia or transient visual loss)
- Jaw or tongue fatigue or pain while chewing
- **ESR >100**



50

Overlap of GCA and PMR

- ~50% patients with GCA have concomitant PMR
- Consider GCA in febrile patient with Buzzwords for PMR...
 - Morning stiffness in proximal muscles of shoulder and hip girdle
 - Gel phenomenon (stiffness with inactivity)



51

Takayasu Arteritis

- Large vessel vasculitis
 - Aorta, carotids and pulmonary arteries
- Buzzwords 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



52

Question #10

- 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 a steroid injection with transient improvement but subsequently developed bilateral ankle pain and redness. She notes subjective chills and sweats.
- She recalls several tick bites in the last 2 months.

53

Question #10

- Exam:
 - T 100.5°F; 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, Anti-CCP Ab negative



54

Question #10

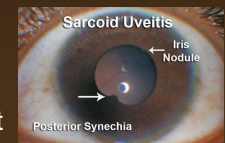
Which of the following is most likely to be diagnostic?

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

55

Sarcoidosis

- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
 - Only form of sarcoid that is a clinical diagnosis
 - Triad of hilar LAN, acute arthritis, EN
 - Women, ankles (>90%), fevers common
- BUZZWORDS
 - Hilar LAN, EN, uveitis, parotid enlargement
 - Non-caseating granulomas
 - Aseptic meningitis with basilar enhancement



56

Erythema nodosuma

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



57

Erythema nodosuma

- **NO** cause >50% of cases
- **D**rugs: sulfonamides, Penicillins
- **O**ral contraceptives
- **S**arcoid (Lofgren's syndrome)
- **U**lcerative colitis (or Crohn's or Bechet's)
- **M**icrobes:
 - EBV, Hep B/C
 - *Streptococci*, *Bartonella*, TB, *Mycoplasma*
 - Endemic fungi



58

Question #11

PREVIEW QUESTION

2025
INFECTIOUS
DISEASE
BOARD REVIEW



- A 19-year-old Iraqi immigrant is hospitalized for 2-day history of fever and abdominal pain.
- He has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the appendix path was normal. Subsequent episodes resolved spontaneously after 2-3 days.
- Exam:
 - T 102.2°F; pulse 114; no rash
 - Abdominal guarding, rebound tenderness, hypoactive bowel sounds
- Labs:
 - WBC 16,650; UA normal
 - BMP & LFTs normal
 - No occult blood in stool
 - CT of abdomen and pelvis normal

59

Question #11

PREVIEW QUESTION

2025
INFECTIOUS
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BOARD REVIEW



What is the most likely diagnosis?

- Hereditary angioneurotic edema
- Familial Mediterranean fever
- Systemic lupus erythematosus
- Crohn's disease
- Acute intermittent porphyria

60

Familial Mediterranean Fever

- Auto-inflammatory disease causing a periodic fever syndrome
 - Others: PFAPA, TRAPS, hyperimmunoglobulin D
- Recurrent attacks of fever & serositis (peritonitis, pleuritis, arthritis) manifesting as pain
- Dx: Genetic testing
- Buzzwords and associations:
 - Periodic fever episodes (PLUS...)
 - Serositis
 - Mediterranean ancestry



61

Question #12

- 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.



62

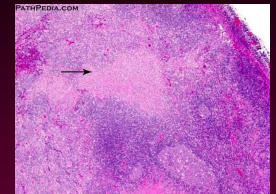
Question #12

- Exam:
 - T 101.4°F; 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

63

Question #12

- Serologic studies:
 - EBV IgM negative
 - CMV, Toxo, *Bartonella* negative
 - RF, ANA, ds-DNA negative
- Lymph node pathology:
 - Necrotizing lymphadenitis with histiocytic infiltrate and phagocytosed debris.
- Stains for AFB and fungi negative



64

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

65

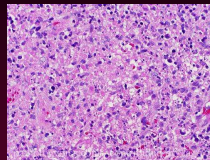
Kikuchi Disease

- AKA acute necrotizing histiocytic lymphadenitis
- Self-limited condition of unknown cause
- Typically occurs in young women
- Fever & cervical LAN (esp posterior, usually unilateral)
- Rarely: morbilliform rash, diffuse LAN, aseptic meningitis, uveitis
- Leukopenia and atypical lymphocytes in 25% of cases

66

Kikuchi Disease

- Diagnosis by pathology:
 - Necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris
- Buzzwords and associations:
 - Acute onset fever and cervical adenopathy in young woman
 - Atypical lymphocytes (mono-like syndrome)
 - Path: necrotizing adenitis with histiocytosis



67

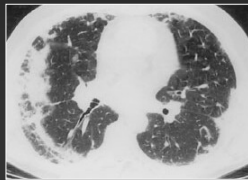
Question #13

- 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.

68

Question #13

- Exam: Temp 101.5°F; 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



69

Question #13

Which one of the following is the most likely diagnosis?

- A. Strongyloidiasis
- B. Disseminated histoplasmosis
- C. Sarcoidosis
- D. Allergic bronchopulmonary aspergillosis
- E. Eosinophilic granulomatosis with polyangiitis

70

EGPA

- AKA Churg-Strauss Syndrome
- 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 infiltrate in setting of difficult to control asthma
- Tapering of steroids often “unmasks” EGPA
- May be p-ANCA positive

71

EGPA

- Buzzwords 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)

72

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Question #14

PREVIEW QUESTION

2025
INFECTIOUS
DISEASE
BOARD REVIEW



- 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 on business
- He has no pets and takes only an OTC decongestant. He denies use of illicit substances, including intranasal cocaine

73

Question #14

PREVIEW QUESTION

2025
INFECTIOUS
DISEASE
BOARD REVIEW



- Exam:
 - T 100.2°F; 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



74

Question #14

PREVIEW QUESTION

2025
INFECTIOUS
DISEASE
BOARD REVIEW



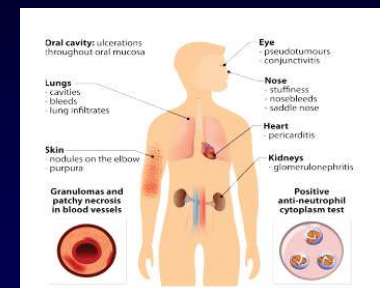
Which of the following will most likely support the diagnosis?

- c-ANCA
- Anti-glomerular basement membrane Ab
- Urine toxicology screen
- Angiotensin converting enzyme (ACE)
- Pulmonary angiogram

75

Granulomatosis with Polyangiitis (GPA)

- Systemic vasculitis of medium and small arteries
- Primarily involves upper and lower respiratory tracts and kidneys
- Variably involves joints, cartilage, eyes, skin, and nervous system



76

Granulomatosis with Polyangiitis (GPA)

Dx:

- Suggestive: Positive ANCA (~85% sensitivity)
IFA: c-ANCA
ELISA: anti-proteinase 3 (PR3-ANCA)
- Diagnostic: Biopsy

Buzzwords and associations:

Nasal symptoms (Saddle nose and perforation)

Lung nodules

Respiratory and renal findings (hematuria)

77

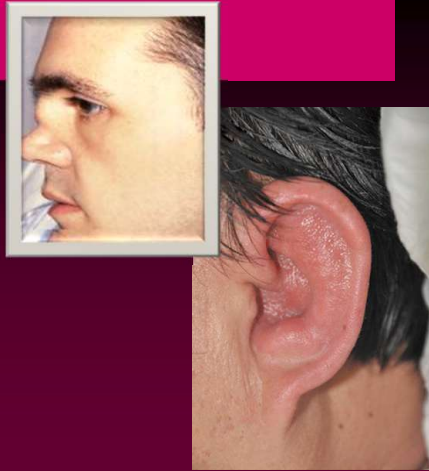
Question #15

- 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

78

Question #15

- Exam:
 - Afebrile
 - Left auricle is inflamed and tender, ear lobe is spared
 - He has a saddle-nose deformity; the nasal mucosa is normal
 - Labs: CBC normal



79

Question #15

What is the most likely diagnosis?

- A. Malignant otitis externa
- B. Leprosy
- C. Granulomatosis with polyangiitis
- D. Relapsing polychondritis
- E. Congenital syphilis

80

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Relapsing Polychondritis

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



81

Saddle-nose Deformity

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



82

Relapsing Polychondritis

- Buzzwords and associations:
 - Recurrent “cellulitis” (cartilage inflammation)
 - Saddle-nose
 - Cauliflower ear
 - Sparing of ear lobe
 - Parasternal joint involvement



83

Karen.bloch@vumc.org



84

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