42 – Syndromes that Masquerade as Infections

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

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Syndromes that Masquerade as Infections

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

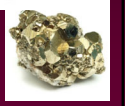
ID Board Content

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%

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

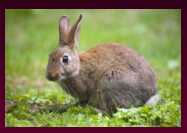


Test taking tip

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

Test taking tip

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



(pulmonary) TULAREMIA

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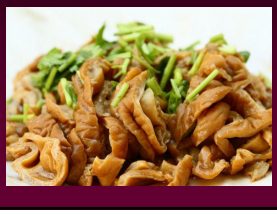
Test taking tip

I say “Chitterlings” (aka chitlins, aka hog intestines)

You say…..



Test taking tip

I say “chitterlings”

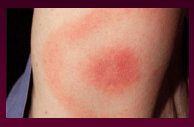
You say…..

YERSINIA (gastroenteritis)

Test taking tip

I say ”Bull’s-eye rash”

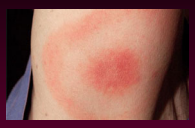
You say…..



Test taking tip

I say ”Bull’s-eye rash”

You say…..



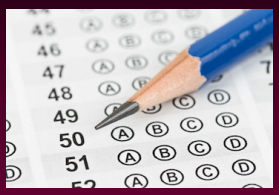
Lyme disease

(or Erythema migrans or STARI)

My Approach to Mimics

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

Examples



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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

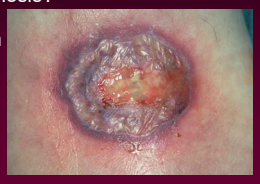
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

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

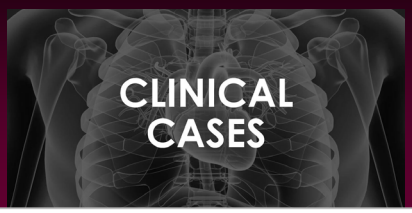
Question 3

A patient has a slowly enlarging ulcerated skin 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



But this being boards…..



To optimize learning : CLOSE THE SYLLABUS

Case 4

- 26yo 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.
- But 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.

Case 4

- Exam:
  - Vitals:
    - T=38.4ºC, 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

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

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)

HLH: Diagnostic Criteria

- At least **5** of the following:
  - Fever
  - Splenomegaly
  - Cytopenias (any line)
  - Hypertriglyceridemia (>3mmol/L)
  - Ferritin >500 mcg/mL
  - Elevated soluble IL-2 receptor (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 5

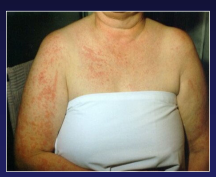
PREVIEW QUESTION

- A 39-year-old woman is admitted for fever for 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.

Physical Exam

PREVIEW QUESTION

- T=104.2º 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.



- Labs: PREVIEW QUESTION
  - 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.

Question 5 PREVIEW QUESTION

- The most likely diagnosis is?
  - A. Lymphoma
  - B. Adult Still's Disease
  - C. Acute Rheumatic Fever
  - D. Cryoglobulinemia
  - E. Kikuchi Disease

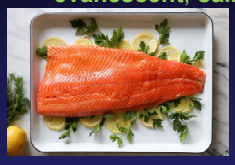
Adult Still's Disease (Adult Onset JRA)

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 Disease

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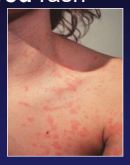


Koebner phenomenon (rash at pressure sites)

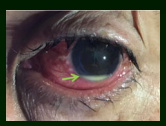
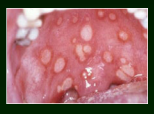
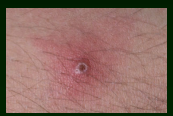
Case 6 PREVIEW QUESTION

- 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.

- 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.

PREVIEW QUESTION

- A 6mm papulo-pustular lesion is present in the right antecubital fossa where they drew blood yesterday in the ED.

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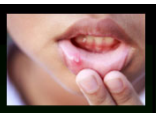
Question 6

PREVIEW QUESTION

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

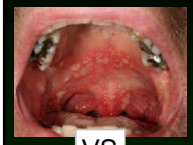
Behçet's disease



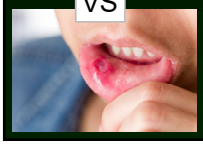
Pleomorphic vasculitis diagnosed clinically

- 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 (abdomenal pain, bloody diarrhea)
  - Aseptic meningitis
  - Arterial and venous thrombosis

Behçet's disease



VS



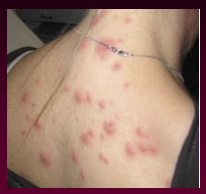
- Ulcers is the buzz word, but the trick is differentiation from infectious causes (HSV, coxsackie, etc)
- Additional Clues
  - Recurrence
  - Ocular findings
  - Pathergy (needle or IV site)

Case 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; P 98, Otherwise unremarkable.
- CBC showed a white blood cell count of 12,250 with 20% bands.

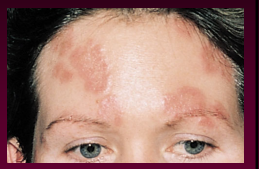
Hospital Day 2:

- 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.



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.

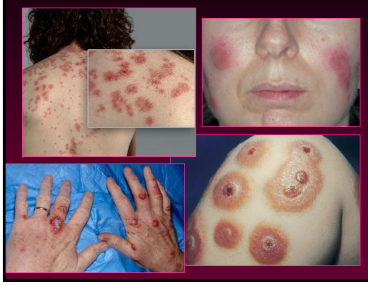
Question 7

- Which 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, 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

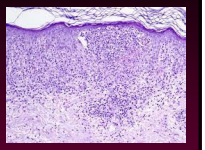
Skin Lesions in Sweet Syndrome



- 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**

Sweet Syndrome

- Buzz words and associations:
  Fever and a rash
  Neutrophilia (peripheral and on path)

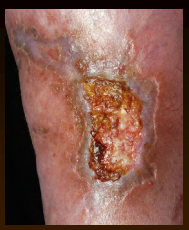


- Be suspicious in patients with malignancy (esp AML), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 8

- 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
- There has been no response to oral antibiotics.
- For the past year he has been troubled by an "upset stomach". On further probing, he describes intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool.

- Exam:
  T 100.2
  Abdo pain to palpation
  Skin lesion



- Labs:
  WBC 11,150 (2% eos)
  ESR=79, CRP=110
  BMP normal
  Chest x-ray normal

Question 8

Which one of the following is the most likely diagnosis?

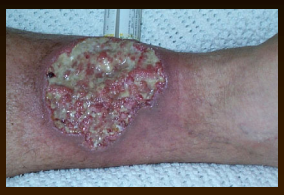
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Cutaneous blastomycosis
E. Squamous cell cancer

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

Pyoderma Gangrenosum

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



Case 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.

- Exam:
  T 102.2, 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

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

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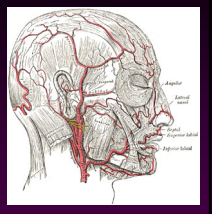
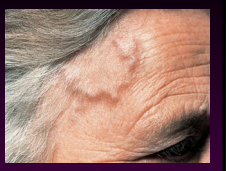
Giant Cell Arteritis

- 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



Giant Cell Arteritis

Buzz words & Associations:



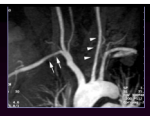
FUO in a patient >50 years PLUS

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

Overlap of GCA and PMR

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

Takayasu Arteritis



- Large vessel vasculitis
  - Aorta, carotids 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 10

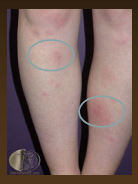
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with a steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness.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

Exam:

T 100.5; 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

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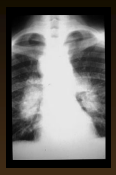
Question 10

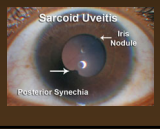
Which of the following is most likely to be diagnostic?

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

Sarcoidosis

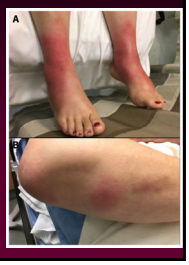
- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Only form of sarcoid that is a clinical diagnosis
  - Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, uveitis, parotid enlargement
  - Non-caseating granulomas
  - Aseptic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





Erythema nodosum

- 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



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- Ulcerative colitis (or Crohn's or Bechet's)
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  - *Streptococci*, *Bartonella*, TB, *Mycoplasma*
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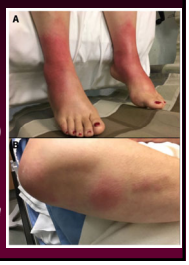


Case 11

- 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; 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

42 – Syndromes that Masquerade as Infections

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

Question 11

The most likely diagnosis is:

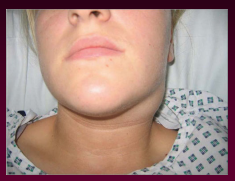
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

- 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
- Buzz words and associations:
  - Periodic fever episodes (PLUS…)
  - Serositis
  - Mediterranean ancestry

Case 12

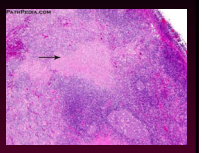
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



- 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 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.



Question 12

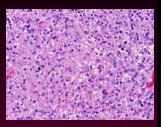
Which one of the following is the most likely diagnosis?

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 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.

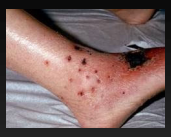
Kikuchi Disease

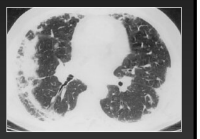


- Diagnosis by pathology:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

Case 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.





- 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. Eosinophilic granulomatosis with polyangiitis

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.

EGPA

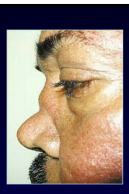
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 14

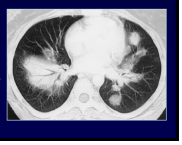
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business.
- He has no pets and takes only an OTC decongestant.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

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.

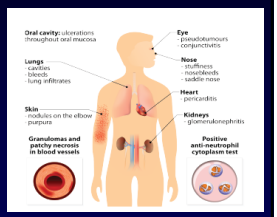


Question 14

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

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.



Granulomatosis with polyangiitis

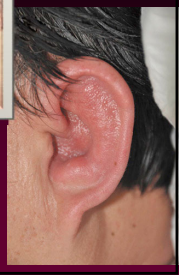
- Dx:
  Suggestive: Positive ANCA (~85% sensitivity)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

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

Case 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.

Case 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

Question 15

The most likely diagnosis is?

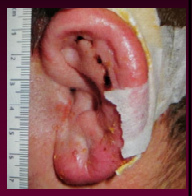
A. Malignant otitis externa
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

Relapsing Polychondritis

--Immune-mediated condition.

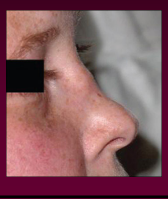
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.

--Clinical diagnosis.



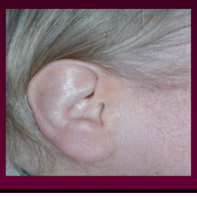
Saddle-nose Deformity

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



Relapsing Polychondritis

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



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