Thieves' Market

American College of Physicians
Leading Internal Medicine, Improving Lives

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No financial disclosures

What is a Thieves' Market?

- Present a case
  - History
  - Physical Exam
  - Lab and imaging studies
  - Reveal diagnosis
- Review teaching points about the case
- Repeat for a second case

Your Role in Thieves' Market

- Steal the diagnosis… but how?
- Interrupt and shout out the diagnosis

Requirements to Win

- Shout out the diagnosis before it appears on the screen!
- Nonspecific diagnoses won't count
- You must say and I must repeat what you said
- I will not confirm whether a guess is correct until the end

What happens if I win?


Let's Do This!

Case 1 History

28-year-old Hispanic woman cc: weakness and chest pain

-3 months
- Recurrent epistaxis
- Anemia
- Nasal procedure
- Nose bleeds less frequent

-1 months
- 2nd trimester miscarriage
- Leakage of fluid → IUFD → misoprostol
- D&C for retained placenta → EBL 1800cc
- Transfused 3 units PRBCs

-1 week
- Fever/chills
- Weakness
- SOB
- Chest pain

Case 1 History

28-year-old Hispanic woman cc: weakness and chest pain

Fever: x1 week, subjective, with associated chills

Weakness: x1 week, diffuse, progressively worsening, unable to get out of bed on her own

Chest Pain: worsened with exertion and deep breaths, alleviated by laying on her side

SOB: x3 days, at rest and with exertion

Review of Systems

Denies

- Blurry vision
- Joint pain
- Lower back pain
- Neck pain/stiffness
- Weight loss/gain
- Cough/wheezing
- Edema
- Heat/cold intolerance
- Anxiety
- Depression
- Skin lumps
- Rashes

Review of Systems

Positive

- Abdominal pain/loose bowel movements x several days
- Headache
- Mild Nausea (no vomiting)

Histories

Medical

Anemia from epistaxis

Surgical

“nasal procedure” for epistaxis

Medications

Ferrous Sulfate 325mg every other day

NKDA

Histories

Family History: listed as “unknown”

Social History:

- Emigrated from El Salvador 3 years ago
- Works cleaning houses
- Denies tobacco, alcohol, or drug use
- No travel outside of Alabama in 3 years

Physical Exam:

T: 100.3°F HR: 130 RR: 16 BP 104/74 O2: 97%

GEN: Female in NAD, appears tired

HEENT: PERRL, EOMI

Neck: No JVD

Chest: CTA B

CV: Tachycardic, regular rhythm, 2/6 holo-systolic murmur at apex

GI: soft, BS+, NT, ND

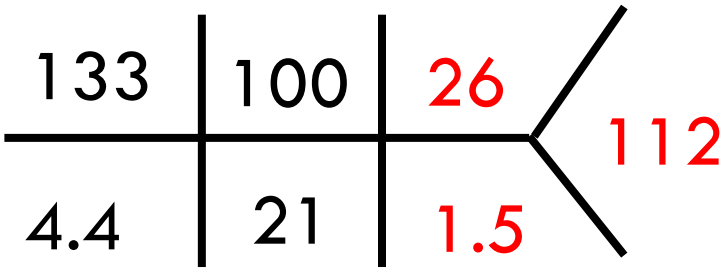
Skin: no rashes

Neuro: difficulty following commands (with interpreter)

strength: 3/5 in BUE and BLE, 5 beats L ankle clonus, brisk 2+ reflexes throughout

Psych: flat affect

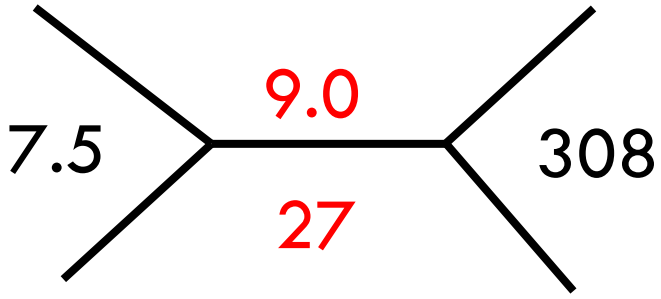
Labs



Ca: 8.2

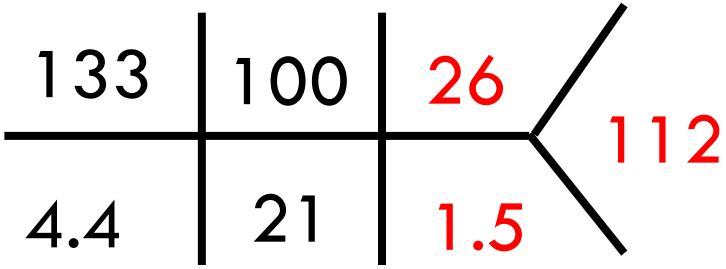
Mg: 2.1

MCV: 81



N: 86% L: 9% M: 4%

Labs



112

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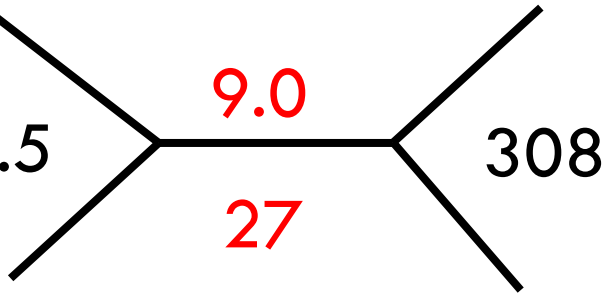

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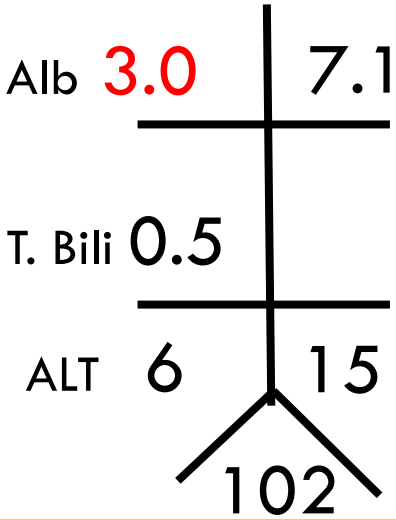


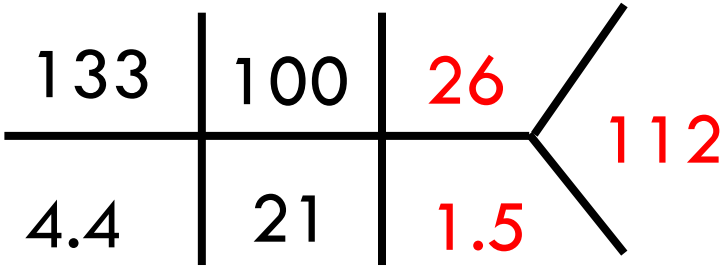
COVID/Flu: neg

HIV: neg

UCG: neg

INR: 1.08

Labs



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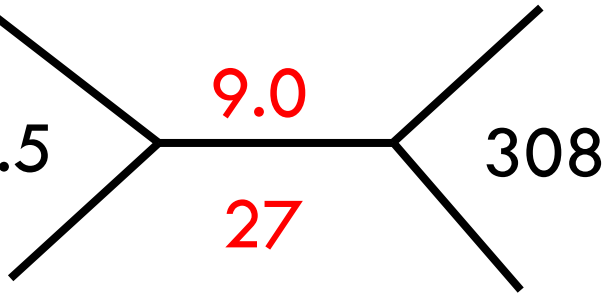
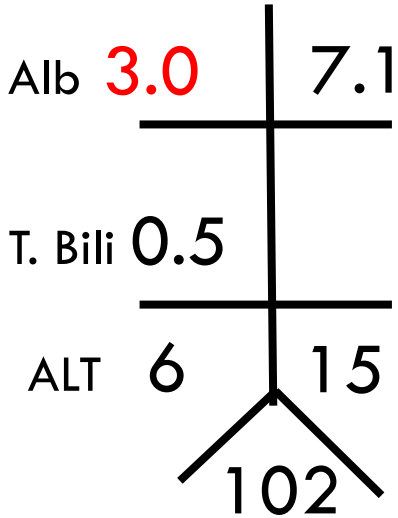


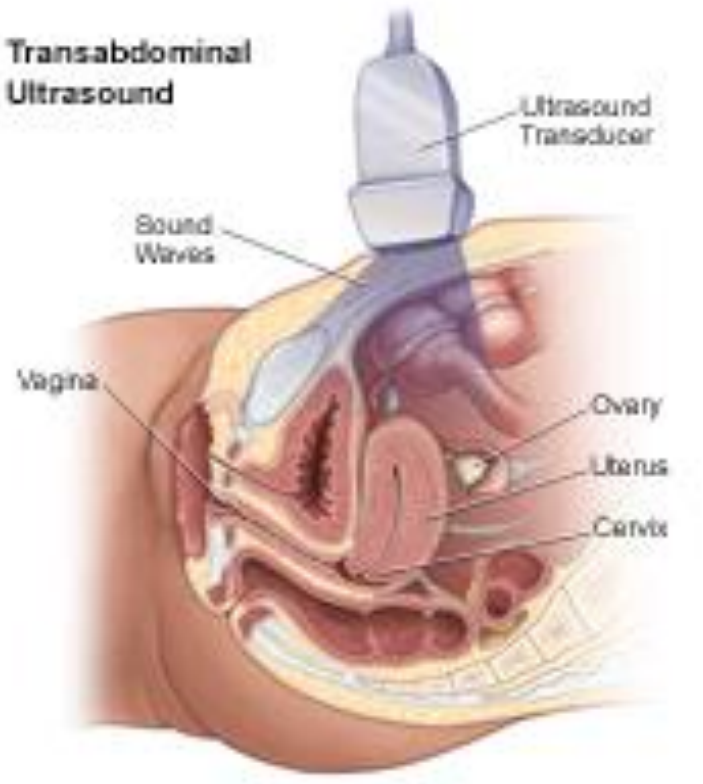


COVID/Flu: neg
HIV: neg
UCG: neg
INR: 1.08

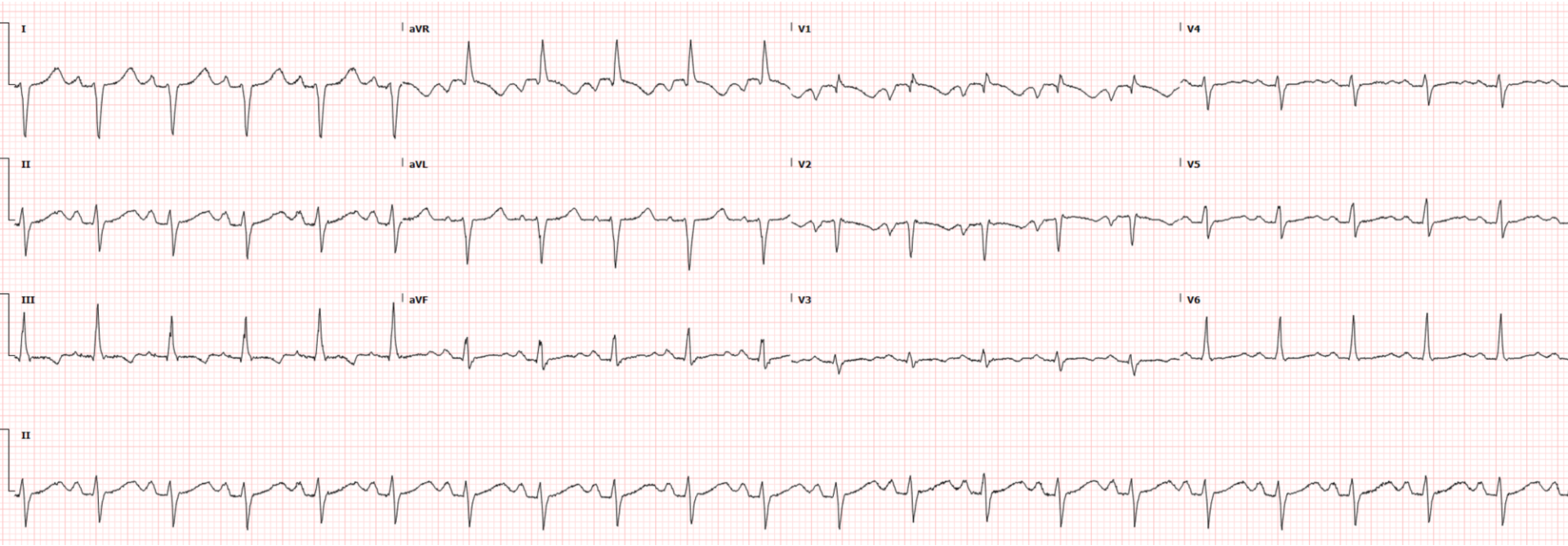
N: 86% L: 9% M: 4%
CRP: 154
ESR: 83
UA: 3+ prot, 3+ blood, >25RBCs, >50WBCs, 12 hyal casts

ER Pelvic US

No convincing sonographic evidence of retained products of conception.



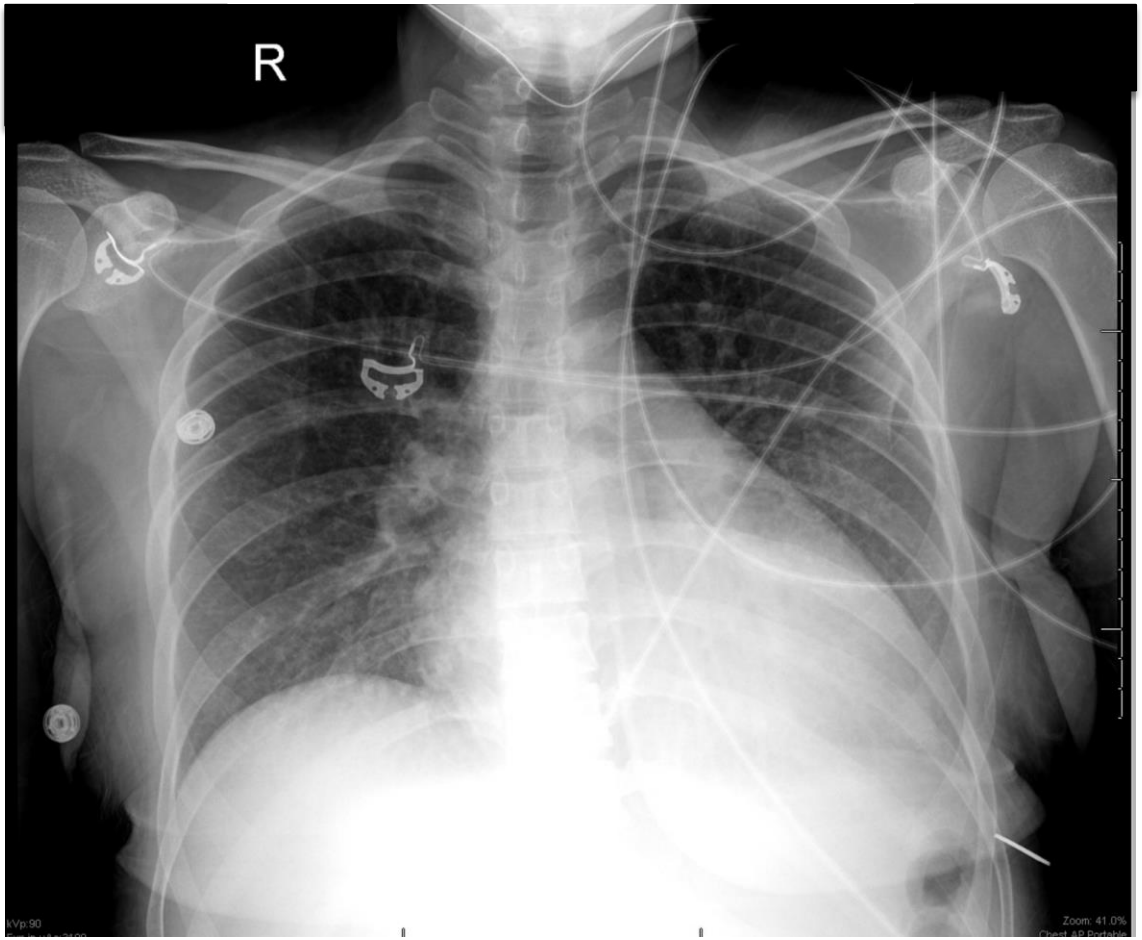
Diagnostic Studies



Sinus Tachycardia, RAD, LA enlargement

Diagnostic Studies

- Moderate cardiomegaly
- Left lower lobe airspace opacity may represent atelectasis. However, superimposed infection is not excluded
- There is perihilar vascular prominence without frank edema.



Labs, continued

BNP: 3,027 (0-100)

HS-Troponin: 663 (3-15)

Given chest pain with elevated troponin admitted to CCU. Admission diagnosis = Sepsis

Diagnostic Studies

Right Heart Catheterization:

1. Normal right sided filling pressures
2. Mildly elevated PCWP & left sided filling pressures
3. Normal SVR
4. Preserved CI by Fick

Left Heart Catheterization:

1. No significant obstructive CAD

Diagnostic Studies

TTE:

- LV Ejection Fraction = 40-45%.
- RV systolic function is normal.
- Normal IVC with >50% collapse with sniff. Estimated RAP is 3 mmHg.
- Mitral valve leaflets: moderately thickened, severe mitral stenosis, mild to moderate mitral regurgitation.
- The left atrium is severely dilated.

TEE: The mitral valve leaflets are severely thickened with what could possibly be thrombus. There is severe mitral stenosis.

Diagnostic Studies

Cardiac MRI

- Severe mitral stenosis.
- Nonenhancing areas along the mitral valve leaflets on postcontrast imaging raise suspicion of *thrombi*

Lupus Anticoagulant (PTT-LA and dRVVT): neg
IgG Cardiolipin: 9
IgM Cardiolipin: 18 (<12)
Beta 2 glycoprotein: IgM <2
Beta 2 glycoprotein: 6

Diagnostic Studies

MRI Brain:

- Numerous foci of restricted diffusion within both the supratentorial & infratentorial brain parenchyma.
- Findings are highly concerning for *embolic infarctions*. There is *diffuse leptomeningeal enhancement* and *papilledema* which is concerning for *meningitis* likely infective etiology.

MRI C-spine:

- No evidence of cord compression or cord signal abnormality.
- MRA Head and neck: unremarkable

Labs

Negative

- Viral respiratory panel
- Blood cultures x 4
- Urine culture
- Throat culture
- Fungal culture
- Histo ag
- Crypto ag
- 1-3 beta-D-glucan
- Tspot TB
- Brucella IgM +, IgG –
- Q Fever IgM, IgG
- Bartonella IgM, IgG
- Trep ab
- ASO

Labs

CSF

- WBC: 3 RBC 29
- Protein: 45 Glu: 46
- Crypto ag: neg
- Culture: negative
- Fungal cx: negative
- Toxoplasma IgG: neg
- West Nile: IgG+, IgM neg

CSF

- VZV, HSV, CMV neg
- Autoimmune & Paraneoplastic ab panel negative

Consults

- Cardiology review of TTE/TEE/MRI
  - Chronic thickening, not vegetation, not thrombi
  - Further history revealed, severe sore throat and fever at age 14
  - MV = chronic mitral stenosis from Rheumatic heart disease

Problem List: 28-year-old woman w/ weakness and chest pain

Explained by RHD

Mitral Stenosis

Left atrial enlargement

Reduced LVEF

SOB/DOE

Problem List: 28-year-old woman w/ weakness and chest pain

Explained by RHD	Unexplained
Mitral Stenosis	Fever
Left atrial enlargement	Weakness/Confusion/Headache
Reduced LVEF	Cerebral emboli
SOB/DOE	Chest Pain/NSTEMI
	Recurrent epistaxis
	Renal Insufficiency
	Anemia
	Elevated inflammatory markers

Consults

- Neurology review of MRI
  - Embolic infarcts are numerous and tiny, more consistent with inflammation/vasculitis

Rheumatology studies

Cryoglobulin: negative

C3: 39L

C4: 7L

CH50: 22L

ANA: +1:640, homogenous

Ds-DNA: +>1:640

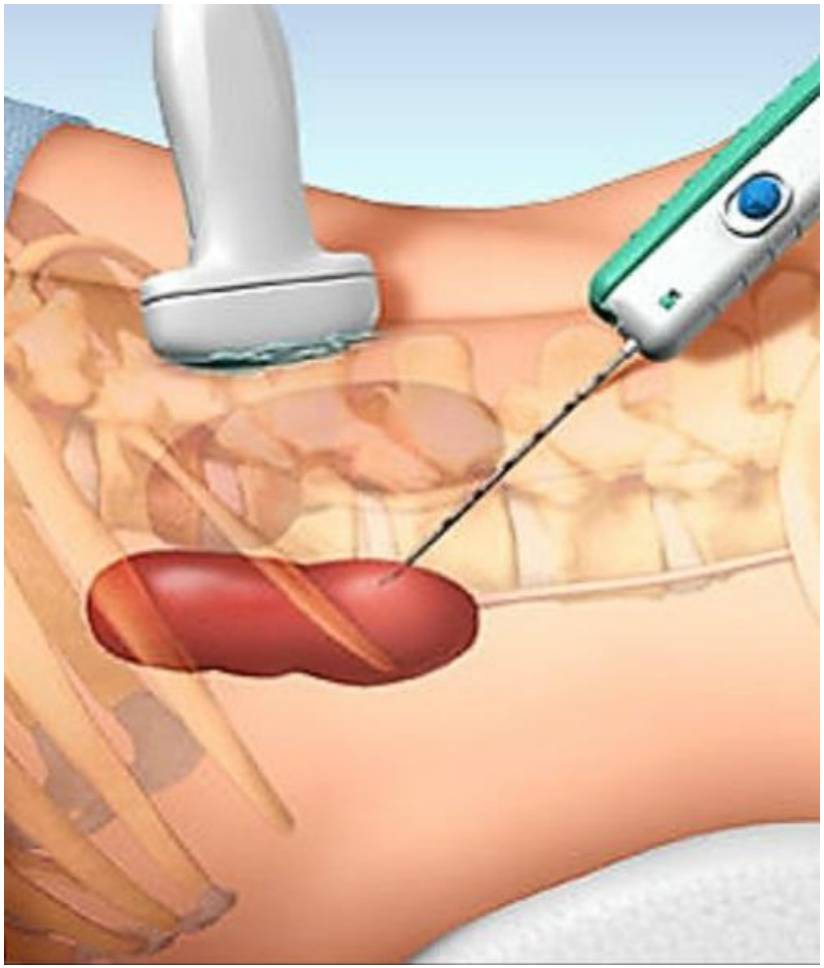
SSA: 63H

SSB: 23H

RNP: 17

Anti-Smith: <12

Renal Biopsy



Focal lupus nephritis (Class IV-S) with focal glomerular necrosis (6/35) and a single crescent (1/35)

Necrotizing arteritis and arteriolar thrombosis, focal.

FINAL DIAGNOSIS

- Systemic Lupus Erythematosus with
  - SLE Cerebritis
  - SLE Nephritis
  - SLE Myopericarditis
- She received 1 gram of methylprednisolone, Cytoxan, and hydroxychloroquine
- Improved strength and resolution of fever/systemic inflammation, kidney insufficiency and confusion … valve replacement soon

Systemic lupus erythematosus (SLE)

- Auto-immune disease of unknown cause
- Average age onset: 16-55yo
- 10:1 Women: men ratio
- In US women prevalence:

Asian, African American, African Caribbean, and Hispanic American >> White individuals

Systemic lupus erythematosus (SLE)

S EROSITIS
O RAL OR NASAL ULCERS
A RTHRITIS IN >2 JOINTS
P HOTOSENSITIVITY

B LOOD DISORDERS
R ENAL INVOLVEMENT
A NA+
I MMUNOLOGIC
N EUROLOGIC SYMPTOMS

M ALAR RASH
D ISCOID RASH

1997 ACR Criteria

- 4 of 11

- Specificity: 93%
- Sensitivity: 82%

Systemic lupus erythematosus (SLE)

The entry criterion is necessary to classify SLE.	
Entry criterion: ▪ ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever).*	
At least 1 clinical criterion required to classify SLE. Additional additive (clinical or immunology) criteria are counted toward th total score.	
Additive criteria: ▪ Do not count a criterion if there is a more likely explanation than SLE. ▪ Occurrence of a criterion on ≥1 occasion is sufficient. ▪ Criteria need not occur simultaneously. ▪ Within each domain (eg, mucocutaneous, complement proteins), only the highest-weighted criterion is counted toward the total score if more than 1 is present.¶	
Clinical domains and criteria	**Weight**
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g per 24 hours	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10
Immunology domains and criteria	**Weight**
Antiphospholipid antibodies	
Anti-cardiolipin antibodies **or** anti-beta-2GP1 antibodies **or** lupus anticoagulant	2
Complement proteins	
Low C3 **or** low C4	3
Low C3 **and** low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody$^{\Delta}$ **or** anti-Smith antibody	6
A total score of ≥10 and ≥1 clinical criterion are required to classify SLE.	
Total score	

2019 EULAR/ACR Criteria

- +ANA & ≥ 10 points
- Specificity: 93%
- Sensitivity: 96%

Diseases associated with a positive ANA

	% with positive ANA
Systemic autoimmune diseases	
Mixed connective tissue disease	100%
SLE:	
▪ Active	98 to 100%
▪ Remission	90%
Scleroderma	95%
Drug-induced LE	80 to 95%
Sjögren's disease	60%
Rheumatoid arthritis	45%
Raynaud phenomenon	40%
Polymyositis/dermatomyositis	35%
Juvenile idiopathic arthritis	15 to 40%
Organ-specific autoimmune diseases	
Autoimmune hepatitis	70%
Primary biliary cholangitis	50 to 70%
Hashimoto's thyroiditis	50%
Graves' disease	50%
Viral infections*	
EBV	
HIV	
HCV	
Parvovirus 19	
Malignancies*	
Lymphoproliferative diseases	
Paraneoplastic syndromes	
Miscellaneous diseases*	
Inflammatory bowel disease	
Interstitial pulmonary fibrosis	

ANA disease prevalence:1%

ANA in Health Individuals

1:40: 32%

1:80: 13%

1:160: 5%

1:320: 3%

Uptodate, accessed 5.29.24. Tan EM, et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum. 1997;40(9):1601.

Rheumatic Fever

- **Group A strep pharyngitis complications**
  - Suppurative: peritonsillar abscess, sinusitis, Otitis Media
  - Nonsuppurative: rheumatic fever, scarlet fever, Acute GN
- **Acute Rheumatic Fever**
  - 500,000 new cases/yr worldwide (low/mid resource countries
  - Fever, arthritis, carditis & valvulitis, Sydenham chorea
- **Rheumatic Heart Disease**
  - 50% of ARF develop chronic immune mediated valve damage
  - ☆MITRAL VALVE is most frequently affected

Kumar R, et al. Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap: A Scientific Statement From the American Heart Association. Circulation. 2020;142:e337-e357.

Case 2

Case 2 History

33-year-old man cc: fevers

-6 months
Fever x 5-7 days
Malaise, cough, myalgia
Decreased appetite
Daughter sick, HBV vaccine

-3 months
Fever x 5-7 days
Malaise, myalgia
Decreased appetite
No sick contacts

-1 month
Fever x 5-7 days
Malaise, myalgia
Decreased appetite
HBV vaccine
Neck LAD

-2 weeks
Upstate New York
X 1 week
Cabin in the woods
Hiking, no known ticks

Has felt normal between febrile periods

Case 2 History, Presentation

33-year-old man cc: fevers

Fever: 100.8 – 103, controlled with acetaminophen

LAD: nodule noted behind ear

Eyes yellow: noticed by family, x 1 day

Headache: (usually has with febrile periods)

Review of Systems

Denies

- Blurry vision
- Weakness
- SOB, wheezing
- Hemoptysis
- Chest pain
- Palpitations
- Abd pain, Naus/vom
- Diarrhea/constipation
- Easy bruising or bleeding
- Joint pain
- Rashes
- Numbness
- Depression/anxiety

Histories

Medical

None

Surgical

none

Medications

none

NKDA

Histories

Family History: Father: DM, Mother: HTN. No family history of malignancy or auto-immune diseases

Social History:

- Born & raised India, PhD in Germany, US 7 years ago
- Infectious Diseases scientist
- Denies tobacco, alcohol, or drug use
- No travel outside of US in 3 years
- Married, 19 month old daughter, daycare

Physical Exam:

T: 101.5°F HR: 112 RR: 18 BP 119/83 O2: 98%

GEN: NAD

HEENT: PERRL, EOMI, mild scleral icterus

Neck: small, right occipital lymph node

Chest: CTA B

CV: Tachycardic, regular rhythm, no M/R/Gs

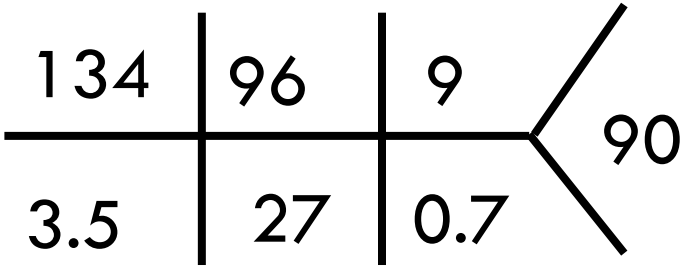
GI: soft, BS+, NT, ND, dullness to percussion LUQ 8cm below costal margin consistent with splenomegaly

Skin: no rashes

Neuro: alert and oriented, no focal deficits

Psych: appropriate mood and affect

Labs



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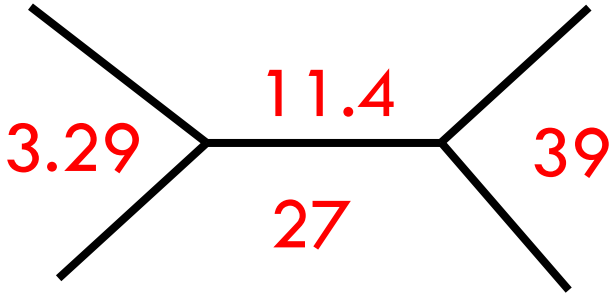
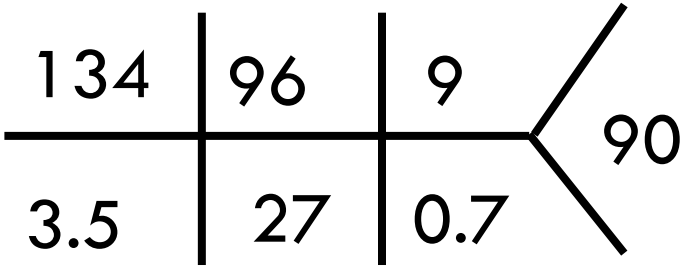


MCV: 80

N: 44% L: 46% M: 6%

Labs



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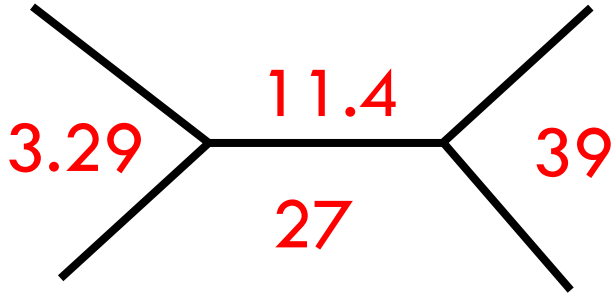

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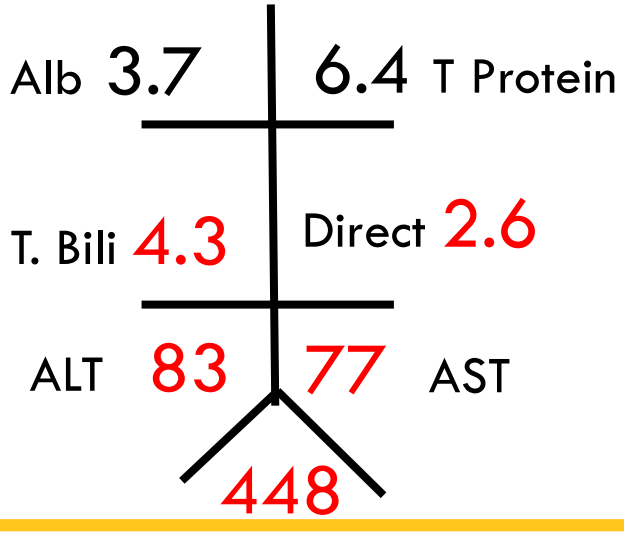

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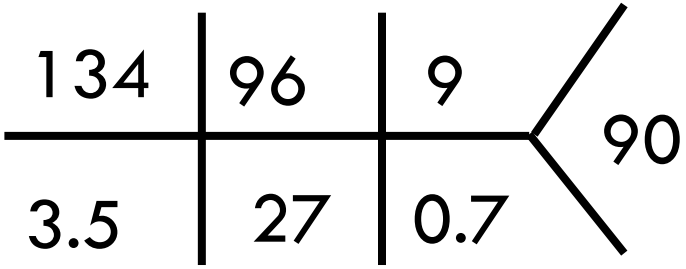

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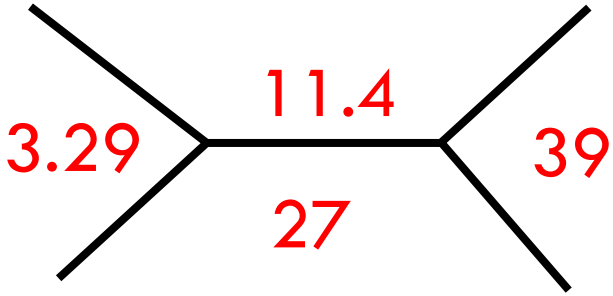

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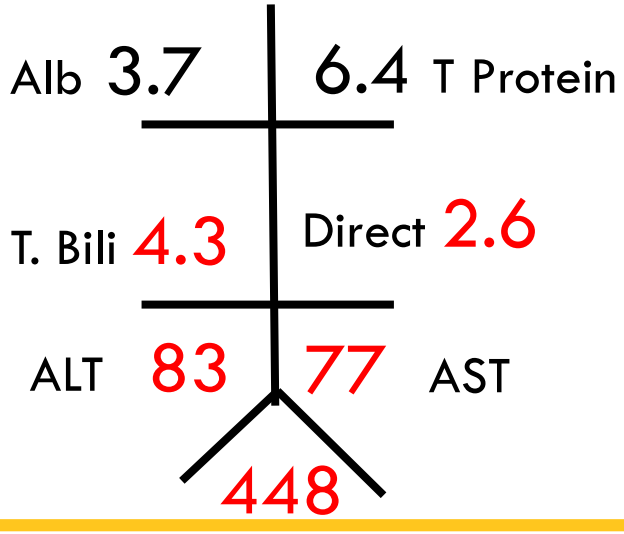


Flu: neg

HIV: neg

INR: 1.16

Acet: <10

CRP: 105

ESR: 9

UA: negative

Labs, continued

Fe: 37

TIBC: 339

Ferritin: 2,277

B12: 391

Folate: >22

Haptoglobin: 88

LDH: 623

Retic: 0.9%

Labs, continued

Fe: 37

TIBC: 339

Ferritin: 2,277

B12: 391

Folate: >22

Haptoglobin: 88

LDH: 623

Retic: 0.9%

D-dimer: 8,011

Fibrinogen: 244

Negative:

ANA

RF

ANCA

CT Chest/Abdomen/Pelvis

- The lungs and pleura are unremarkable
- Bilateral axillary, mediastinal, hilar and subcarinal lymphadenopathy. 2-3cm lymph nodes
- Lymph nodes throughout abd/pelvis enlarged (up to 5 cm
- Mild Hepatomegaly
- Splenomegaly (17cm)

- Gallbladder, adrenals, kidneys, bladder, prostate, GI tract appendix all unremarkable. No bone lesions

Flow Cytometry

Peripheral Blood:

- No evidence of a monoclonal lymphoid or aberrant myeloid population.

Infectious Disease Labs

Negative

Crypto serum

Histo Ag

TSPOT

Lyme IgM, IgG

Brucella IgM, IgG

B Henselae IgG

RMSF IgM, IgG

Ehrlichia IgM, IgG

1-3 Beta D Glucan

Blood cultures

Toxo IgM, IgG

HSV PCR

CMV Ag

CMV IgM

EBV IgG+, IgM –

Hep A,B,C

Bone Marrow Biopsy

- Normocellular marrow (70%) with trilineage hematopoiesis
- No granulomas (Fite, AFB stains, GMS neg)
- No morphologic evidence of dysplasia
- Decreased storage iron
- No evidence of overt hemophagocytosis
- Flow cytometry negative

Excisional Lymph Node biopsy

-Lymph node with T-zone expansion and CD8 dominant T-cell population, favor reactive process, EBV positive.

- No evidence of a monoclonal lymphoid population.

Labs continued

EBV peripheral blood: 105,282 Int units/ml

IL-2 Soluble receptor: 1905 pg/ml (<1033)

FINAL Diagnosis

Hemophagocytic Lymphohistiocytosis (HLH) and Chronic Active Epstein-Barr Virus (CAEBV)

Hemophagocytic Lymphohistiocytosis (HLH)

- A syndrome of *excessive inflammation* and tissue destruction due to *abnormal immune activation*.
  - Triggers: infections, malignancies, rheumatologic disorders
  - Involves the absence of normal downregulation by activated macrophages and lymphocytes

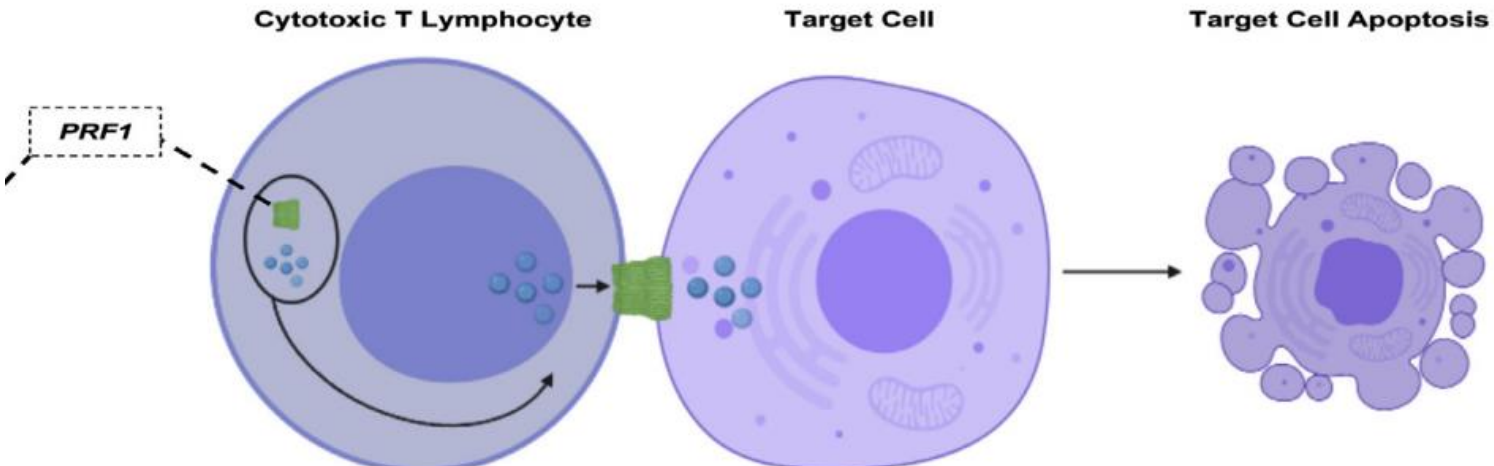
HLH Diagnostic Criteria (5 of 9)

1. Fever ≥38.5°C
2. Splenomegaly
3. Bi-cytopenia or pancytopenia
4. Hypertriglyceridemia
5. Hemophagocytosis in bone marrow, spleen, lymph node,or liver
6. Low or absent NK cell activity
7. Ferritin >500 ng/mL (usually >2,000)
8. Elevated soluble CD25 (soluble IL-2 receptor)
9. Elevated CXCL9

Case 2 continued

Whole Genome Sequencing: homozygous c.1349C>T (p. T450M) missense variant in *PRF1 (perforin) gene*

Perforin: pore forming protein produced by T cells and NK cells to cause apoptosis in target cells and regulate immune response



Case 2 continued

Whole Genome Sequencing: homozygous c.1349C>T (p. T450M) missense variant in *PRF1 (perforin) gene*

Perforin: pore forming protein produced by T cells and NK cells to cause apoptosis in target cells and regulate immune response

PRF1 mutation= cannot clear EBV, overactive immune response

Godby R, Kraemer RR, et al. Co-Occurrence of Familial Hemophagocytic Lymphohistiocytoisis Type 2 and Chronic Active Epstein-Barr Vrius in Adulthood. Am H Med Sci 2020.

Case 2 continued

- Treated with Rituximab
- HSCT recommended
- Fulminant HLH → critical illness
- Transfer to NIH → HSCT, patient died of complications

Godby R, Kraemer RR, et al. Co-Occurrence of Familial Hemophagocytic Lymphohistiocytoisis Type 2 and Chronic Active Epstein-Barr Vrius in Adulthood. Am J Med Sci 2020.

THE END

THE END

Thanks to all for playing along!