A rheumatologist's perspective of Fever of Unknown Origin

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Washington Chapter ACP Annual Meeting

November 2025

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Disclosures

- Participated in Janssen advisory board in 2023

Objective

- What is FUO?
- Approach to evaluating FUO
- Cases!
- Around the world and my final thoughts

Definition of FUO

- “I know it when I see it”
- 1907 – fever lasting 2+ weeks = “long fever”
- 1961 – Petersdorf & Beeson – T 38.3C or higher for at least 3 weeks without a diagnosis despite 1 week of inpatient investigations
  - Durack & Street – 3 inpatient days or 3+ outpatient visits
- No consensus
- Core features:
  - No identified cause of fever
  - Completed reasonable investigations
  - Fever has persisted long enough to rule out self-limited fevers
- Modern definition: Unexplained fever despite high-quality diagnostic work-up after a reasonable amount of time has passed to rule out self-limiting fevers *

* Haidar & Singh. *N Engl J Med* 2022

Evolution of FUO causes over time

- Overall perception: Autoimmune, autoinflammatory > infectious
  - Causes vary by country, type of hospital, patient population
  - Infections remain leading cause*
    - Association between lower income regions and infections
  - ~51% remain undiagnosed
    - More likely in higher-income regions (?over-represent challenging cases?)
- FUO classification
  - Classic (today's talk)
  - Nosocomial (ICU / non-ICU)
  - Immunodeficiency-associated
  - Organ and hematopoietic-cell transplant recipients
  - Neutropenic patients
  - Patients with HIV / AIDS (untreated)
  - Travel-associated

*Gaeta GB et al. *Nucl Med Commun* 2006
*Fusco et al. *BMC Infect Dis* 2019

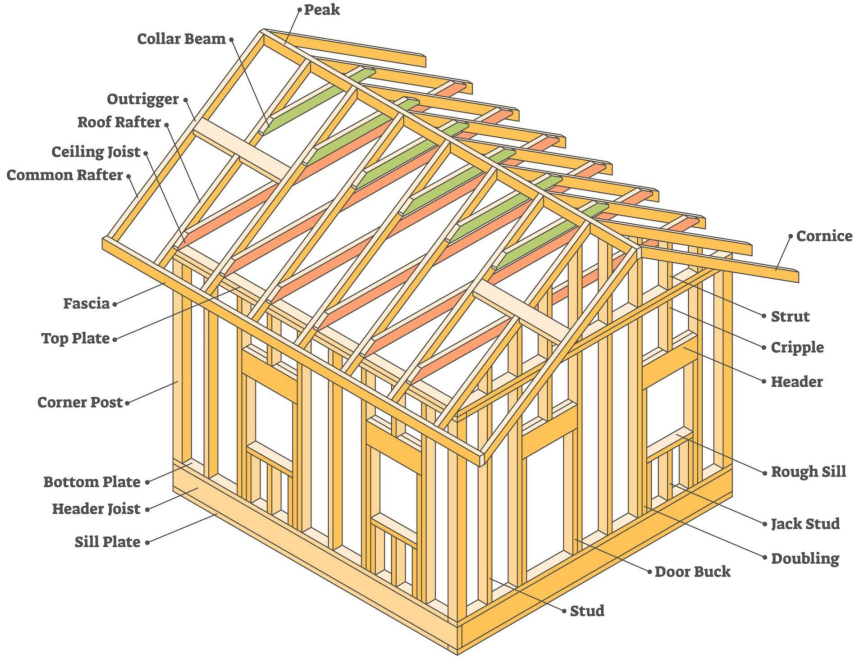
FUO: Autoimmune & autoinflammatory disorders

- 22.2 - 32% of FUO cases *
- Autoinflammatory = disorders of innate immunity w/ dysregulated IL-1B responses / IL-18 responses
  - Ie periodic fever syndromes
- Autoimmune = driven by type 1 interferon response, adaptive immunity
  - Ie lymphoproliferative syndrome
- Mix of both
  - Ie. Adult-onset Still's disease, polymyalgia rheumatica
- Many diagnoses are clinical and based on set criteria w/out gold standard test…
- No clues that specifically indicate rheumatologic cause, but… more frequently occur in: **
  - pts >65
  - inflammatory arthritis
  - skin rash
  - lymphadenopathy
  - Longer fever duration

*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
*Yenilmez E et al. *Int J Clin Pract* 2021
*Gaeta GB et al. *Nucl Med Commun* 2006
*Fusco et al. *BMC Infect Dis* 2019
**Mulders-Manders, CM, et al. *Best Pract & Research Clinical Rheum* 2016

Very basic framework

- Rule out infection
- Consider malignancy
- Consider “common” rheumatologic diseases
- Look for Zebras!



Detailed proposed diagnostic algorithm

Minimal initial eval: history (meds, travel, diet/animal exposures), exam (esp joints, skin, lymph nodes)

↓

Confirm fever, withhold antibiotics if stable and not neutropenic

↓

Determine need for hospitalization

↓

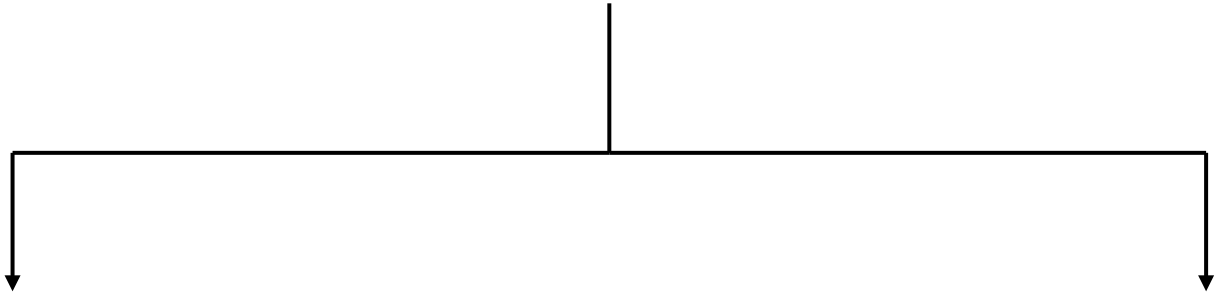
Minimal next eval: basic labs (CBC, CMP), blood cx, HIV, echo, CT c/a/p (and other regions prn)
Consider d/c'ing new/potentially offending meds

↓

Advanced eval: (based on history/exam, epidemiology, exposures, imaging, above lab results):
zoonotic/ tickborne illness, endemic mycoses, viral hepatitis, tuberculosis,
or *testing for rheumatologic and thyroid disorders* *(e.g. RF, ANA, TSH)*
Consider biopsy (rash, temporal artery, lymph nodes, masses, etc) as appropriate

↓

Haidar & Singh. *N Engl J Med* 2022



Diagnosis made

- Treat accordingly
- Consider empiric course of doxycycline, anti-fungal therapy, or tuberculosis therapy if high suspicion

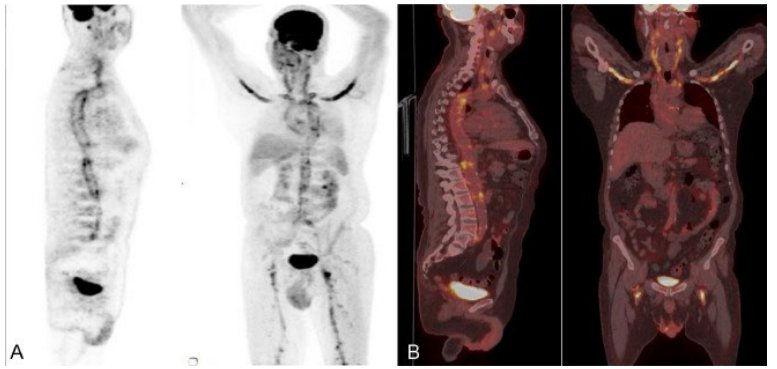
No diagnosis

- Re-evaluate clinical status, history. Consider factitious fever
- Perform new testing based on above
- Perform FDG PET-CT if not already done
- If additional tests are unrevealing, consider metagenomic testing to assess for infection
- Consider empiric anti-inflammatory therapy if not contraindicated
- Consider informing pt that up to 50% of FUO do not have a diagnosis

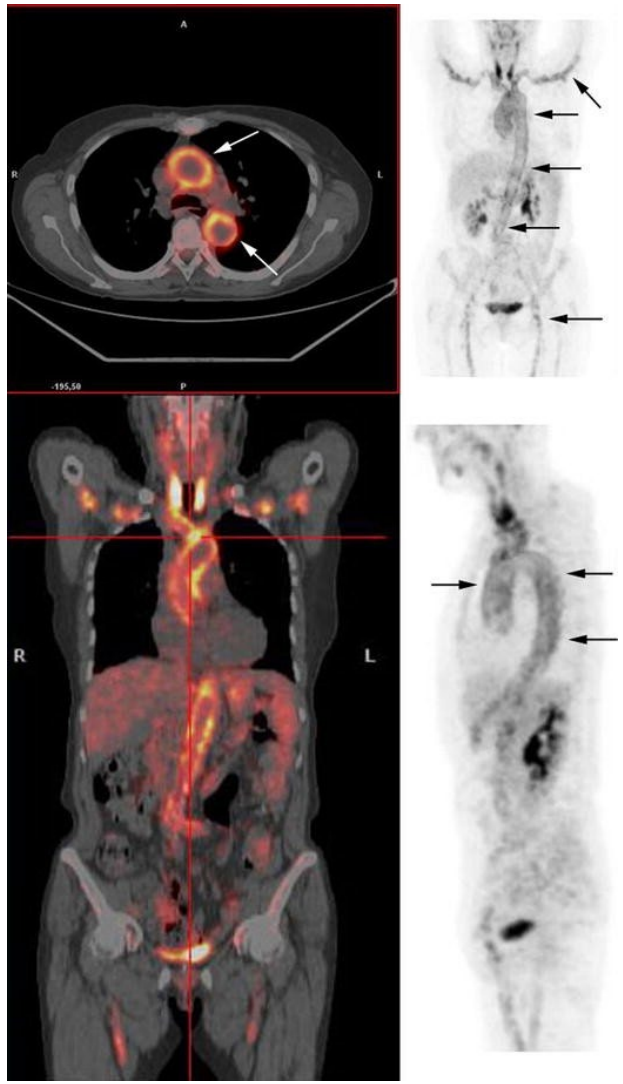
Haidar & Singh. “Fever of Unknown Origin.” *N Engl J Med* 2022

FDG PET-CT

- F-fluorodeoxyglucose positron-emission tomography and CT *
  - Sensitivity: 86-98%
  - Specificity: 52-85%
  - Diagnostic yield = 50% (at least 30% greater than conventional CT)
  - Performance is better in patients with infections, malignancy
- Negative FDT PET-CT scans → high likelihood of spontaneous remission of fever



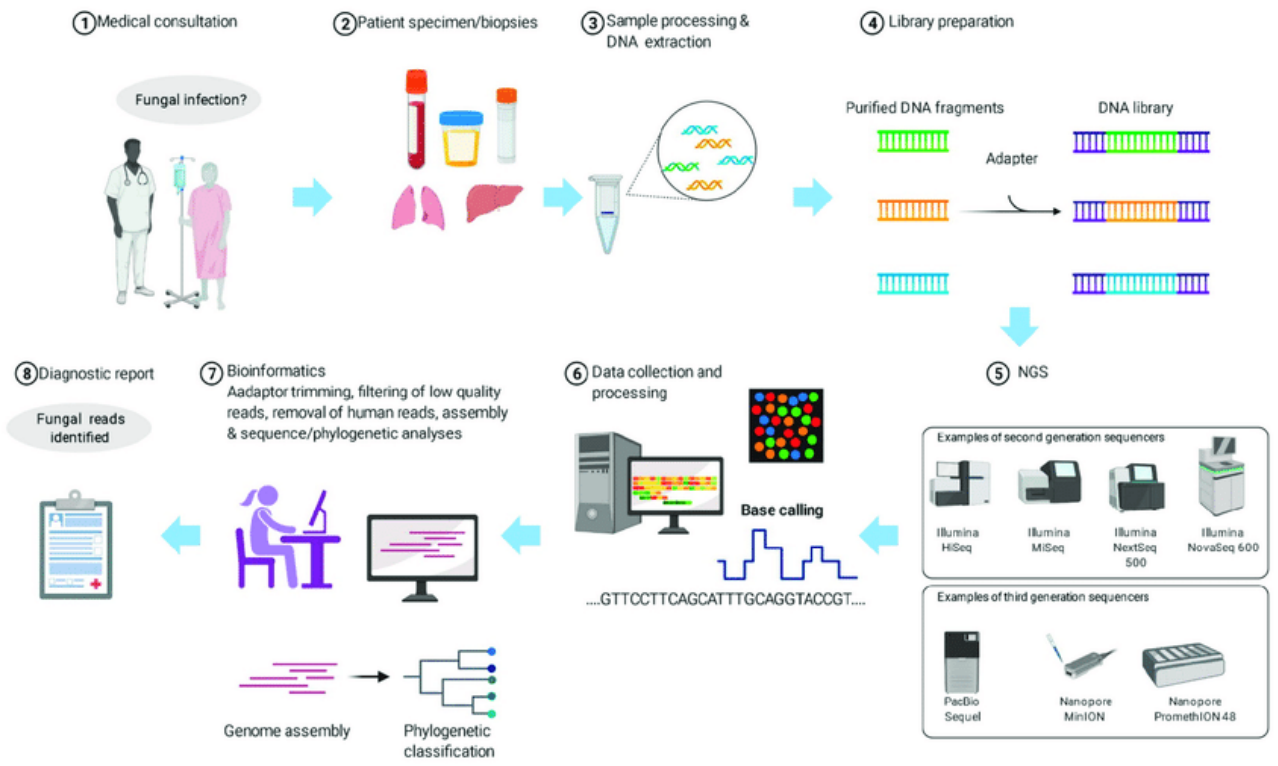
FDG PET-CT scan in patient with large vessel vasculitis



* Bharucha T et al. *Clin Radiol* 2017

Next generation-sequencing

- Next-generation sequency – “unbiased sequencing of all genetic material in a specimen” (bacterial, fungal genomes) *



* Wright WF et al *Clin Infect Dis* 2021

Words of warning…

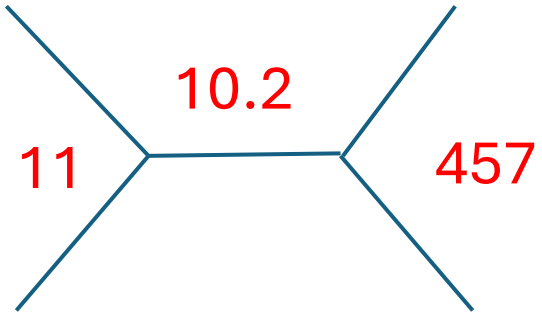
- The Red Herring: Diagnostic clues may be misleading
- Many FUO syndromes are due to uncommon manifestations of common conditions
- Consider the pre-test probability of any condition before ordering the test

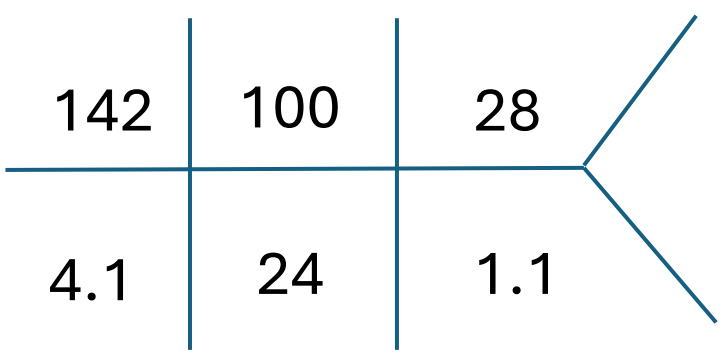
Cases!

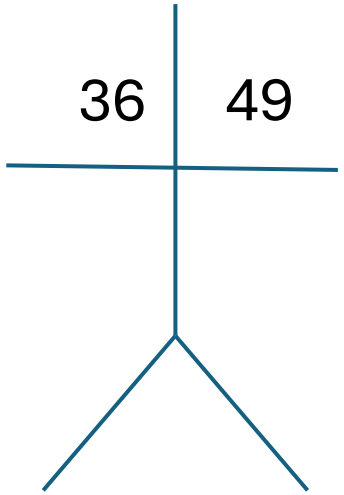
Case 1

- 78 yo male retired fireman w/ h/o prostate cancer and hypertension presents to PCP with 6 weeks of daily fevers 100-101F, whole body pain and stiffness – “it feels like I’m dying”
- Daily fevers up to 101F, lost 22 lbs
- No headaches, vision changes, jaw pain, chest pain, SOB
- Up to date on age-appropriate malignancy screening
- Lives on property in Newberg. No recent travel, known exposures
- P/E: T 100F, HR 96, BP 150/90
- Appears tired, non-toxic. Needs help getting up from chair
- Very painful with shoulder abduction, limited hip ROM

Case 1: data





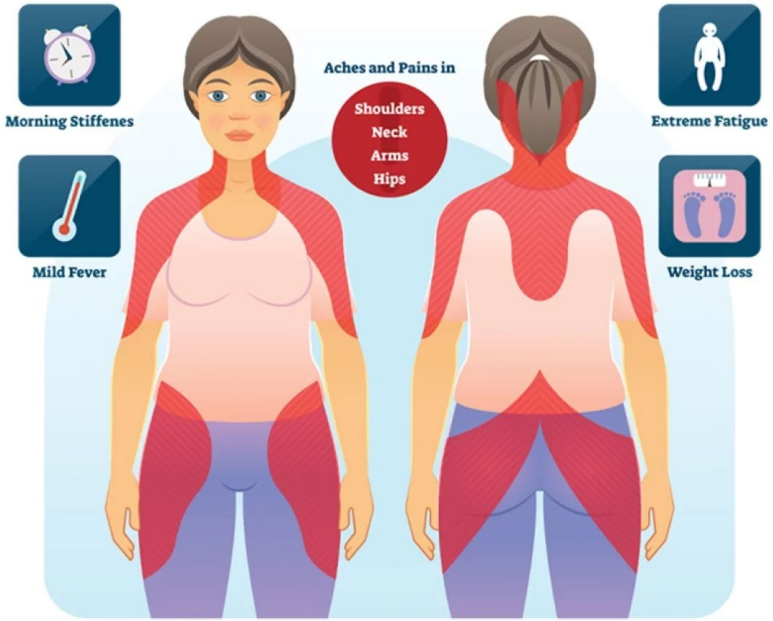


Patient's values	Normal range
ESR 91	< 20 mm/hr
CRP 17	< 0.3mg/dL
RF 5	< 20 U/mL
Anti-CCP 7	< 20 U/mL

"Could this be PMR??"

Excellent response to 15mg of prednisone!

FUO: Polymyalgia Rheumatica (PMR)



- 7.3% of autoimmune FUO cases *
- 19% of PMR patients with fever **
- Inflammatory arthritis, bursitis, enthesitis
- Clinical diagnosis
  - Abrupt onset b/l proximal upper and lower extremity *stiffness/achiness*
  - Age > 50
  - Elevated inflammatory markers (ESR, CRP)
  - 100% response to low dose steroid (~20mg of prednisone)
- Associated with rheumatoid arthritis, Giant Cell Arteritis

*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
** Lien, M. et al. *Seminars in Arthritis and Rheumatism*, 2024 Oct.

SOMEHOW YOU GOT PHOTOBOMBED DURING YOUR X-RAYS!
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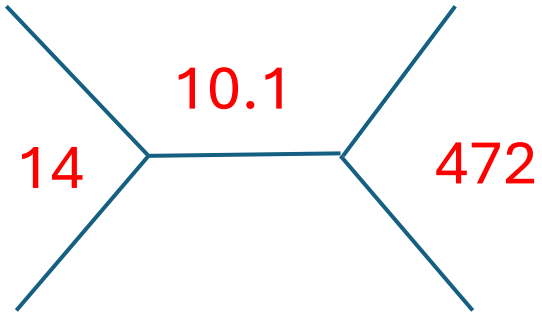
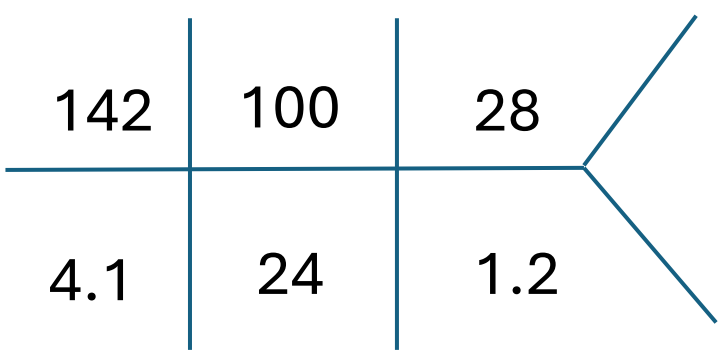
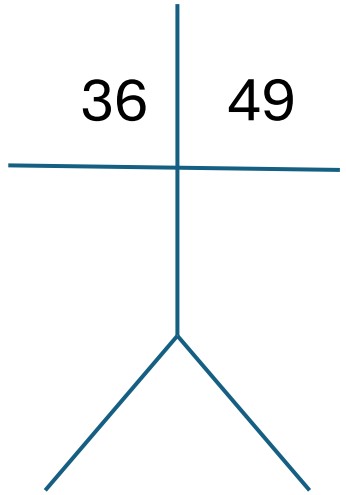
Case 2

- 63 yo female p/t ED with 2 week h/o daily fevers to 103F, 17 lbs weight loss, diplopia.
- Also experiencing daily headaches, right arm pain
- Stiff and achy in arms and legs
- Saw ophtho last week – unremarkable exam
- P/E: T 102.7F, HR 98, BP 150/90 (LUE); BP 96/50 (RUE)
- Appears tired, non-toxic. Needs help getting onto exam table
- Tender along temples
- Diminished R brachial pulse

Case 2: data

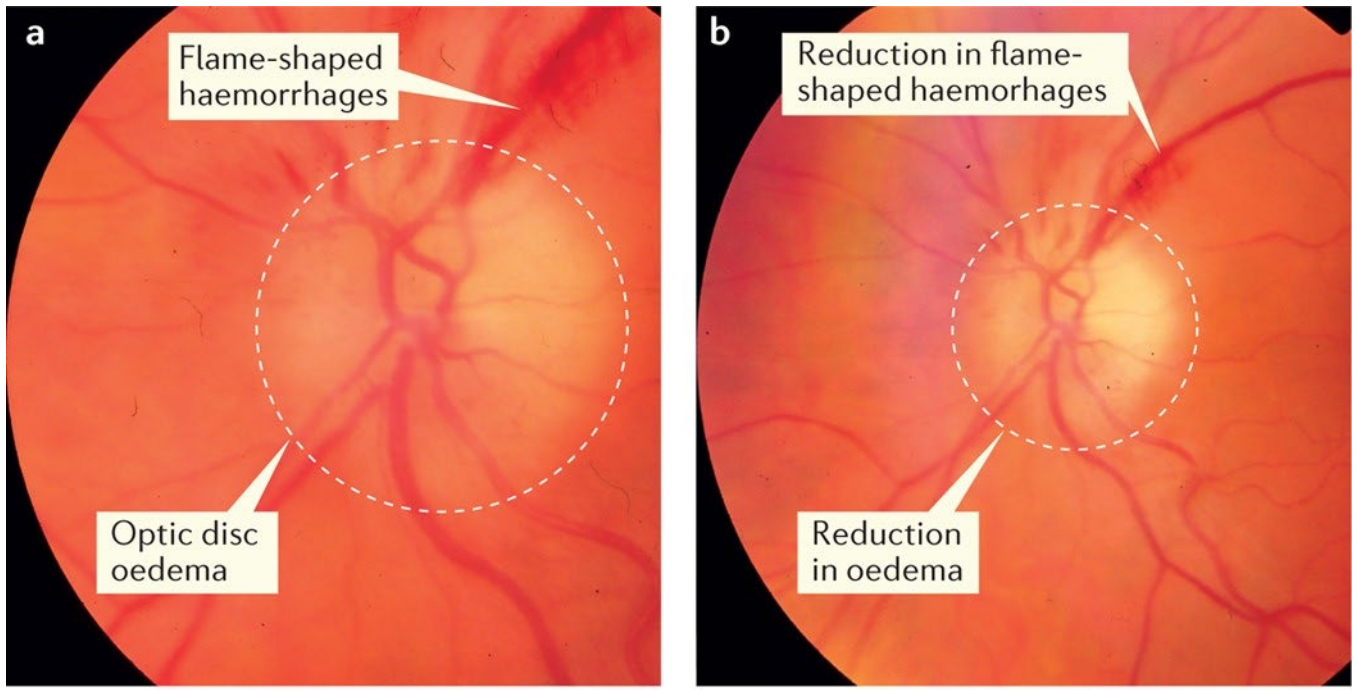






Patient's values	Normal range
ESR > 120	< 20 mm/hr
CRP 37	< 0.3 mg/dL
RF 5	< 20 U/mL
Anti-CCP 7	< 20 U/mL
ANA 1:360	< 1:80

Temporal artery biopsy: Focal and segmental transmural inflammation of the arterial wall. Multinucleated giant cells within the internal elastic lamina, causing disruption of the wall. Mixed inflammatory infiltrate with lymphocytes, histiocytes, occasional eosinophils. There is intimal thickening with luminal narrowing.



Nature Reviews | Rheumatology

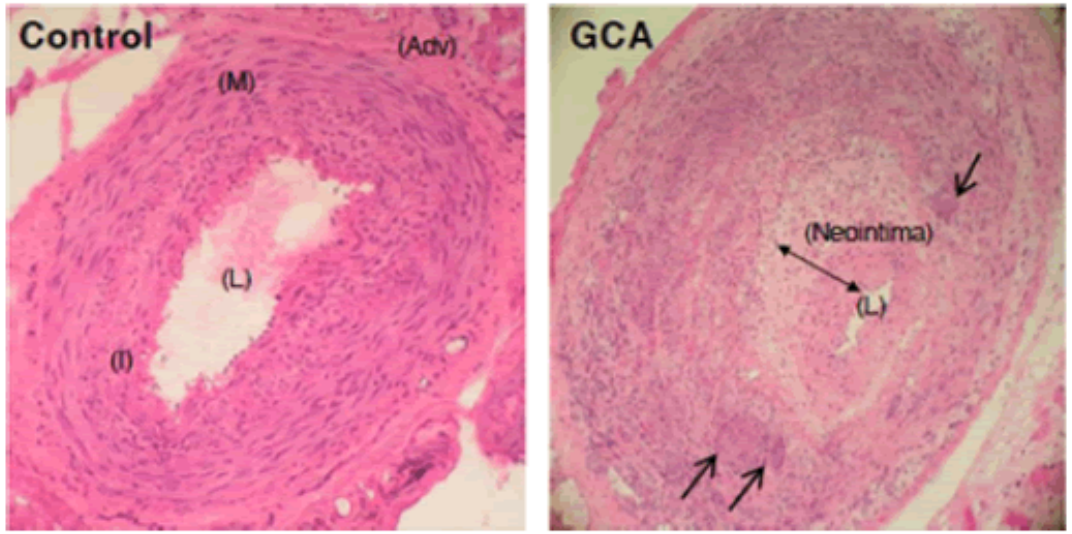
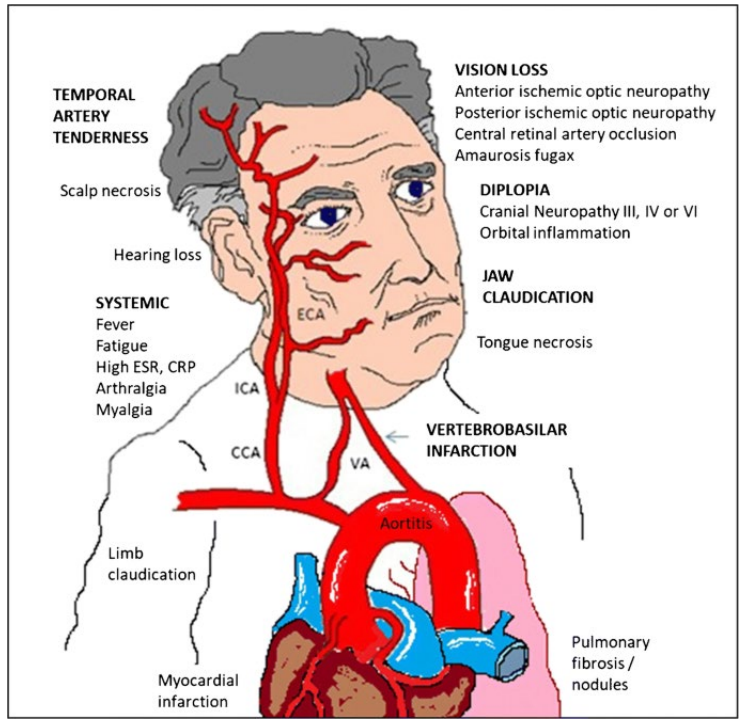


Figure 1: Normal temporal artery biopsy (left) as opposed to a temporal artery biopsy from a patient with giant-cell arteritis (right) disclosing typical transmural mononuclear cell infiltration, internal elastic lamina breakdown and intimal hyperplasia. Double head arrow remarks the thickened intima and single head arrows indicate the presence of giant-cells. Haematoxylin-eosin staining. L: lumen; I: intima; M: media; Adv: adventitia.

FUO: Giant Cell Arteritis

- 11.4% of autoimmune FUO cases *
- 25-51 % of patients w/ GCA have fever **
- Large vessel vasculitis
- Diagnosis
  - Abrupt onset temporal headache(s), vision change (diplopia, amaurosis fugax, blurred, etc), jaw claudication, other s/s of large vessel ischemia
  - Age > 50
  - Elevated inflammatory markers (ESR, CRP)
  - Associated with polymyalgia rheumatica (~50%)
  - Temporal artery biopsy
  - Utility of imaging: temporal artery ultrasound, CTA



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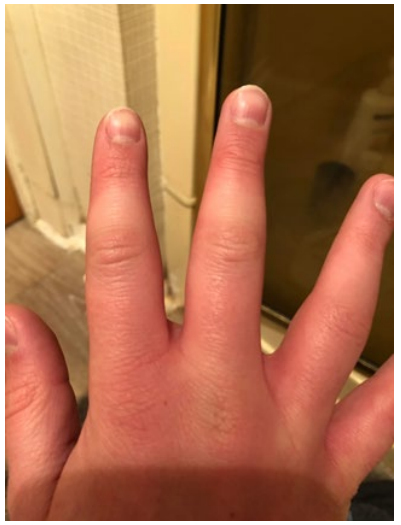
*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
** Fabrizio, C. et al. *Drugs Aging,* 2008.

I'm afraid this is the only way to find the cause of your claustrophobia...
MRI
Ell
Eom 23

Case 3

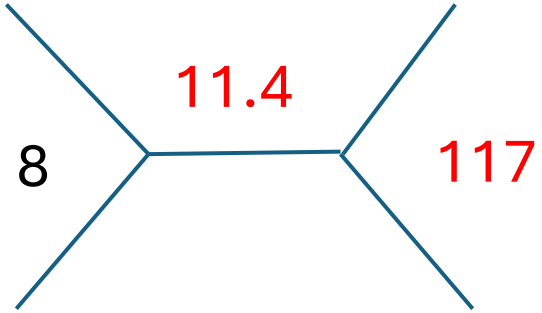
- 21 yo female p/t ED w/ 9 days of daily fevers to 102F, sore throat, headache, abdominal cramping
- UC #1 – (-)Covid, flu. HR 113, T 102F
- UC #2 – persistent fever, (-)viral panel, strep, mono. ESR wnl, CRP 153, PCT 0.6. AST 146
- Rx w/ amoxicillin per PCP for ?UTI
- Overall achy, dysphagia x3 days, rash
- Joints started to swell in fingers
- Returns to ED

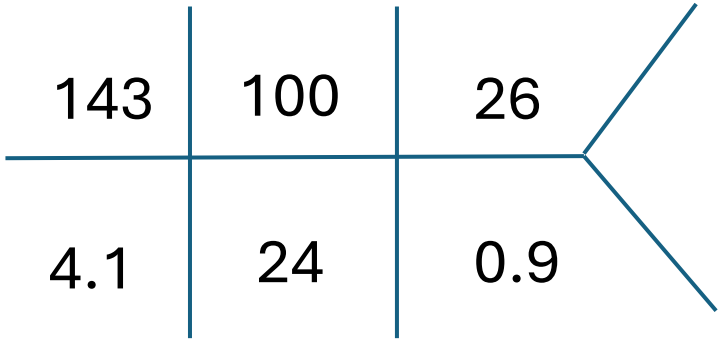
Case 3 data

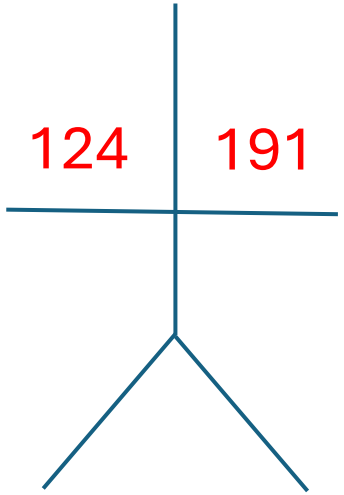


- P/E: T 102.9F, HR 138, BP 104/59
- Appears ill, miserable
- HEENT: tender cervical LNs, no oral ulcers, mildly dry mucous membranes
- Cardiac: tachycardic, regular rhythm, +1/6 systolic murmur
- Pulm: crackles in bases, no wheezes
- Ab: diffusely tender, no guarding, no hepatosplenomegaly
- Skin: diffuse coalescing erythematous macular, mildly papular rash
- MSK: tenderness and synovitis of b/l PIPs, MCPs, wrists, elbows. B/l warm moderate knee effusions, effusions of b/l ankles, MTPs

Case 3: data







Patient's values	Normal range
(-)HIV, CMV, EBV, HCV, Covid, treponema pallidum ab	
Quant gold - indeterminate	Negative
(-) Gonorrhea/ chlamydia	
(-) Blood cultures	
Troponin I, HS 2,211	< 15 ng/L

Case 3: data, continued

Patient's values	Normal range
(-)ANA, dsDNA, C3 / C4 wnl	
ESR > 120	< 20
CRP 35.6	< 0.3
Ferritin 6,668	24-307 ng/mL
LDH 578	105-233 U/L
Triglycerides 317	< 150 mg/dL

- CT soft tissue of neck: small foci of air in palatine tonsil region, likely represents trapped air. No e/o abscess, tonsilitis
- CT chest/ab/pelvis: no acute process in lungs, ab, pelvis. No LAD
- MRI cardiac: no myocarditis. Trace L pleural effusion, no pericardial effusion. Trace tricuspid and mitral regurgitation

FUO: Adult Onset Still's Disease

- 22.8% of autoimmune FUO cases *
- 100% of cases of FUO have fever **
- Clinical diagnosis: (Yamaguchi Criteria – at least 5 features)

Major criteria (at least 2)	Minor criteria
Fever of 39C x at least 1 week	Sore throat
Inflammatory arthralgias / arthritis	Lymphadenopathy / splenomegaly
Evanescent, salmon-pink maculopapular rash, non-pruritic	Liver dysfunction
Leukocytosis (greater than 10K), at least 80% granulocytes	(-)ANA, (-)RF

  - Highly elevated ferritin, ESR, CRP
- Fear of evolution into MAS (macrophage activation syndrome)

*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
** Berardicurti, O. et al. *Rheumatology*, 2021

NOW SERVING!

HUMBLE PIE

DO YOURSELF A FAVOR
&
HAVE A SLICE OR TWO!

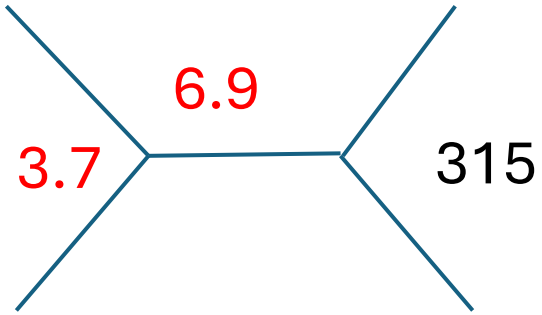
Case 4

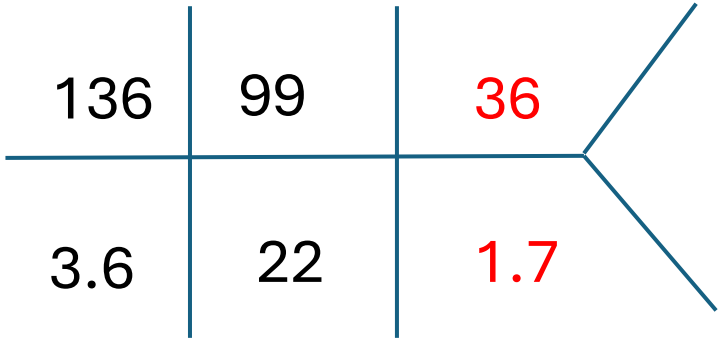
- 74 yo Vietnamese male w/ Thalassemia and HTN p/t ED w/ 3 weeks of fevers and 2 days of nausea, vomiting
- Multiple hospitalizations over the past year – FUO
  - Uveitis
  - Colitis / SBO
  - Periorbital edema
  - Retropharyngeal edema
  - Ear swelling
- Various cytopenias
- Lost 30 lbs over the past year
- GI – colitis and SBO resolved; normal EGD/colonoscopy
- Hematology/ oncology – anemia, weight loss, LAD
  - CT c/a/p w/ nonspecific mediastinal and hilar LAD, persistent anemia
  - Rec bone marrow biopsy
- Ophthalmology – dx w/ uveitis
- Infectious disease – it's not an infection

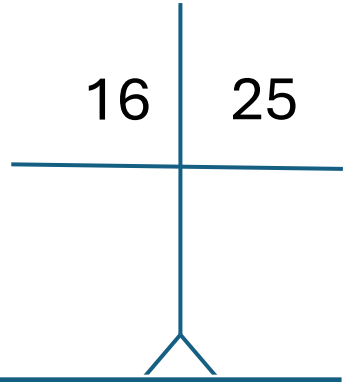
Case 4: P/E

- T 101F, HR 94, BP 148/73
- Appears tired, uncomfortable
- HEENT: tender, swollen R parotid gland, periorbital edema
- Cardiac: mildly tachycardic, reg rhythm, 1/6 sys murmur
- Pulm: scattered basilar crackles, no wheezes
- Ab: mildly tender, no guarding, normal bowel sounds
- Skin: erythematous patches on trunk, extremities
- MSK: no swollen/tender joints

Case 4: data







Patient's values	Normal range
UA: 3-4 WBCs, 11-25 RBCs, 1+ protein, 1+ blood	
ESR 120	ESR < 20
CRP 17.3 mg/dL	CRP < 0.3 mg/dL
Ferritin 969	24-336 ng/mL
IgG4 = 1,810	2-96 mg/dL
(-)ANCA, ANA, RF, cryoglobulins, ACE	
(-) HIV, treponema/RPR, quant gold	
SPEP – possible monoclonal immunoglobulin in gamma region	No monoclonal spikes present

Case 4: data, continued

- Kidney biopsy = patchy interstitial inflammation, focal global glomerular sclerosis, interstitial fibrosis

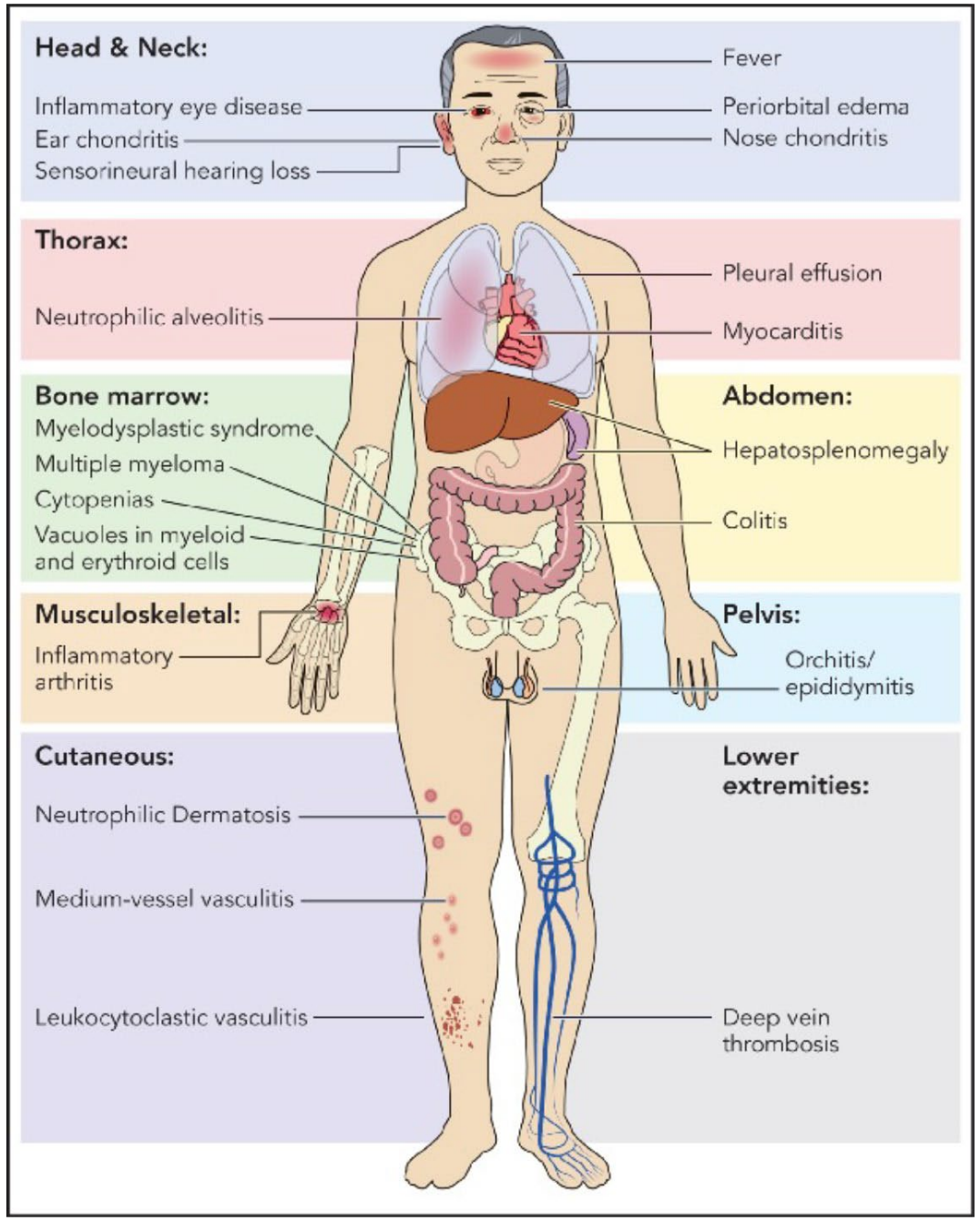
- Bone marrow biopsy = hypercellular (50-60%) w/ myeloid predominant trilineage hematopoiesis, mild myeloid / megakaryocytic dysplasia, blast <1%, increased storage iron, polyclonal plasmacytosis

- Genetic test – UBA1 mutation

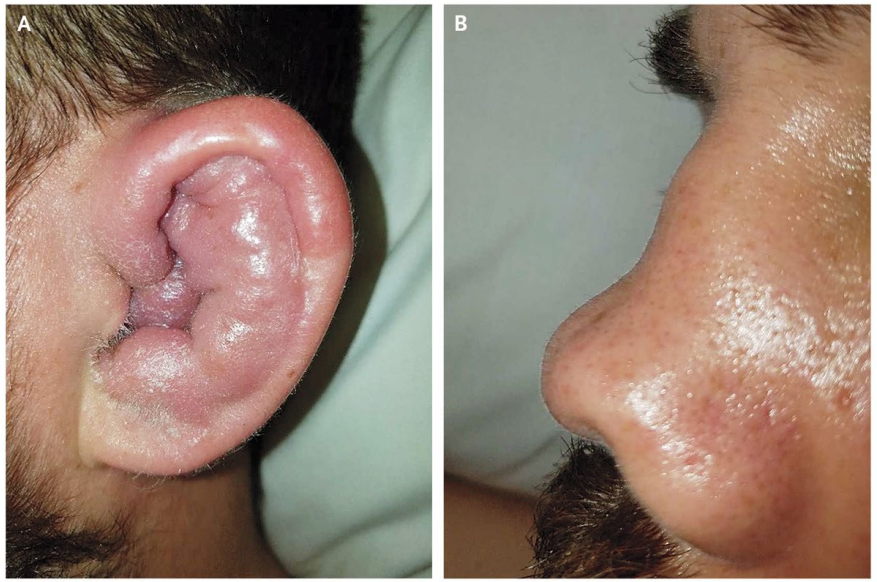
FUO: VEXAS Syndrome

- ?% of FUO autoimmune cases [likely unknown, under-represented]
- 92% of patients with recurrent fever; 64% fever is the presenting symptom *
- First discovered in 2020
- Adult-onset inflammatory disease due to UBA1 genetic mutation
- Diagnosis
  - Multi-system (skin, cartilage, lungs, heart, eye, etc) autoimmune attack
  - Cytopenias (esp macrocytic anemia)
  - Bone marrow biopsy – vacuoles in myeloid and erythroid precursor cells
  - UBA1 genetic mutation (blood test, send to OHSU Knight Cancer Institute)
- Consider in middle-aged to older men, multi-organ inflammation

* Kouranloo et al. *Rheumatology International,* 2024



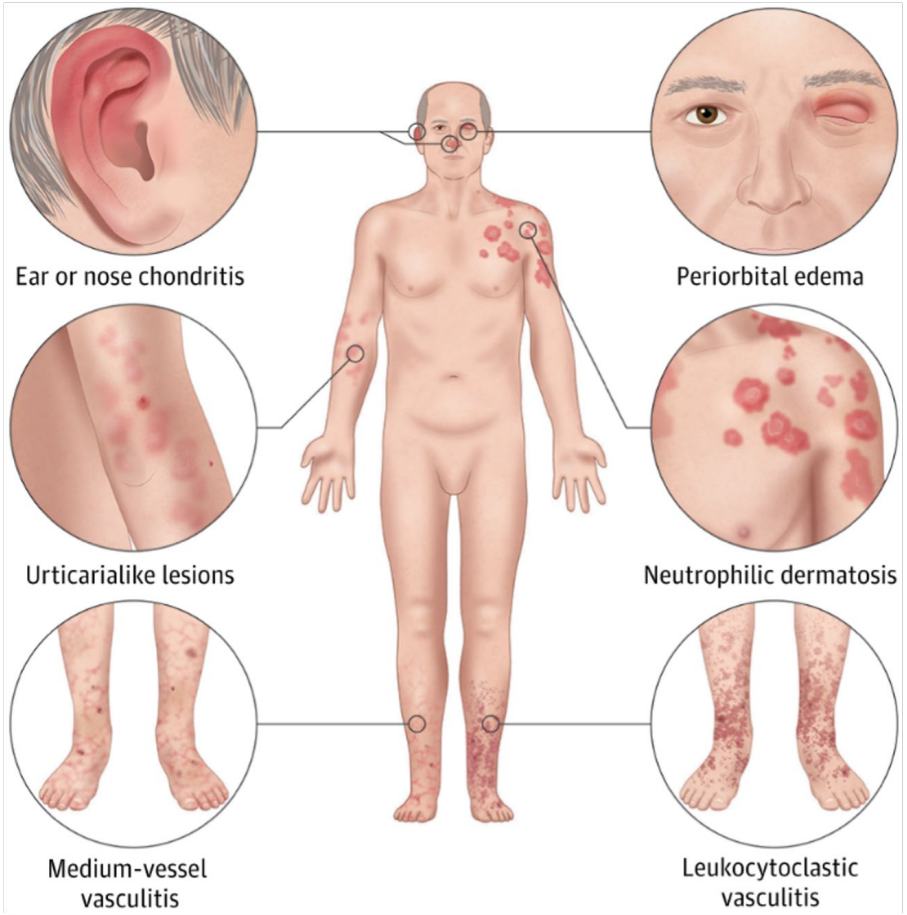
- VEXAS – emerging systemic autoinflammatory disease



National Institute of Arthritis and Musculoskeletal and Skin Diseases

FUO: VEXAS Syndrome

- Cutaneous manifestations



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Case 5

- 28 yo African American female G1P0 22 weeks pregnant presents to ED with fevers, shortness of breath, chest pain, light-headed
- Daily fevers to 101.7F for 2 weeks, improves w/ Tylenol, then recurs.
- Short of breath all the time, has to rest after walking across a room
- Chest pain is pleuritic, positional
- Non-itchy rash on legs. Legs are swollen

Case 5: P/E

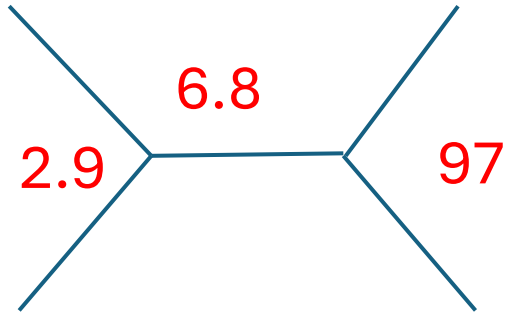
- T 102F, HR 112, BP 92/68
- Appears tired, uncomfortable, anxious
- HEENT: non-tender cervical lymphadenopathy, dry mucous membranes, oral ulcer on soft palate, good dentition

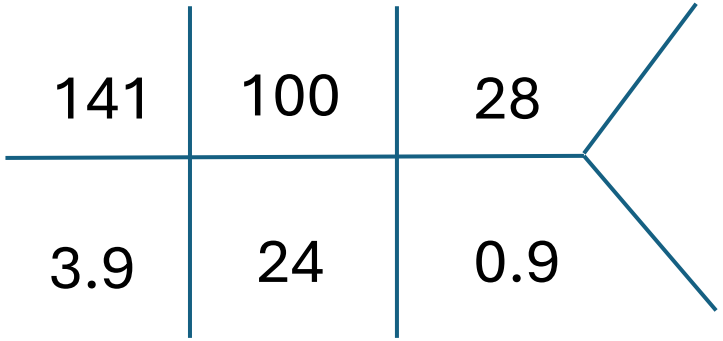
- Cardiac: tachycardic, reg rhythm, 1/6 sys murmur. 2+ lower extremity pitting edema
- Pulm: diminished breath sounds in b/l lower 1/3 of lungs, no wheezes

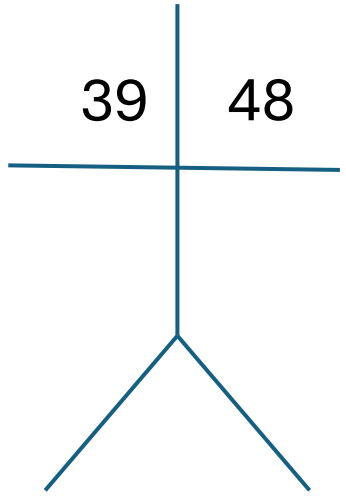
- Ab: gravid, no guarding, normal bowel sounds
- Skin: erythematous patches on lower extremities
- MSK: tenderness/synovitis of PIPs, MCPs, wrists, elbows. Small warm effusions in knees, ankles

Case 5 data

Patient's values	Normal reference
+ANA 1:1280	< 1:80
+dsDNA 572	< 10 IU/mL
+Smith 17	< 7 U/mL
+SSA 226	< 7 U/mL
C3 62	88-201
C4 7	15-45
UA: 1+ protein, 0 RBCs, 1-2 WBCs	







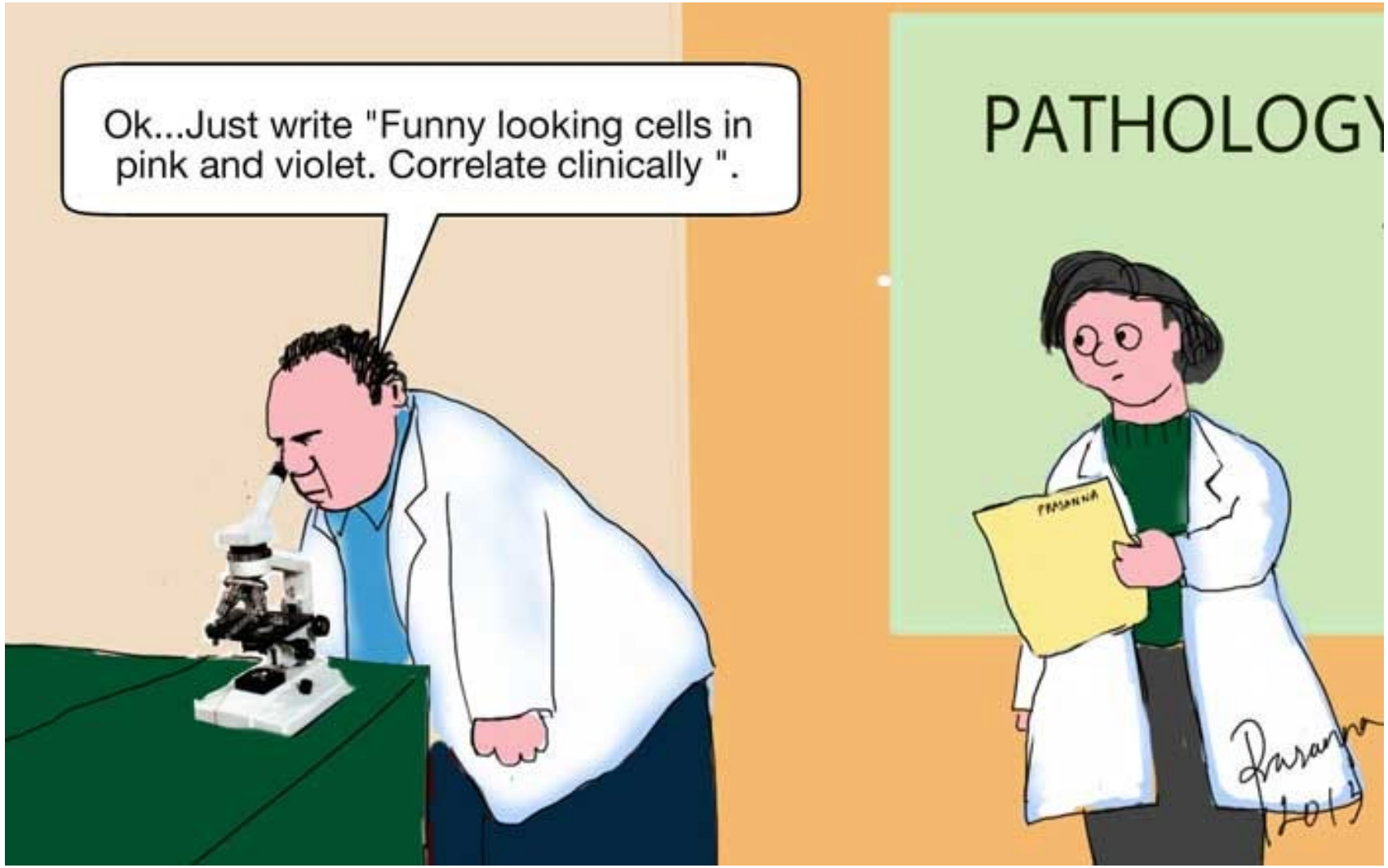
Echo: moderate pericardial effusion, no tamponade
CTPA: no PE; moderate b/l pleural effusions

Lymph node bx: reactive follicular hyperplasia w/ areas of necrosis

FUO: Systemic lupus erythematosus

- 11.1% of autoimmune FUO cases *
- 41.9 % of patients with SLE report fever **
- Diagnosis
  - Serologies: +ANA; +dsDNA, Smith, hypocomplementemia
  - Cytopenias
  - Serositis
  - Nephritis
  - Cutaneous, mucocutaneous
  - Inflammatory arthritis

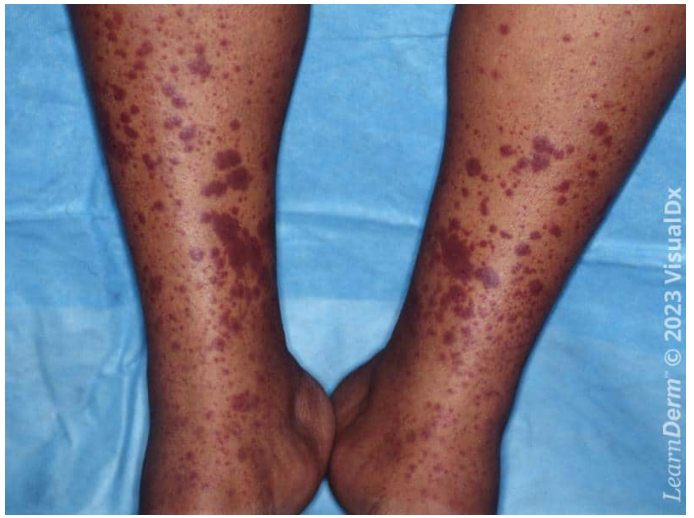
*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
**Olivieri, G. et al. *Clin Exp Rheumatol*, Nov 2022.


Ok...Just write "Funny looking cells in pink and violet. Correlate clinically ".
PATHOLOGY

Case 6

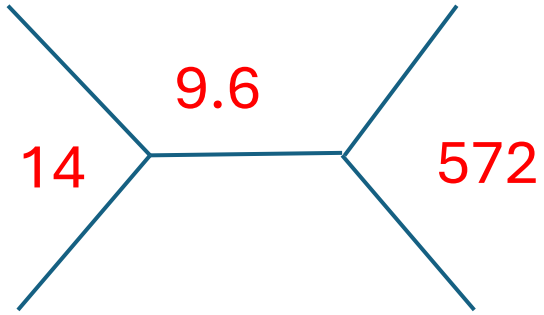
- 68 yo Hispanic male farmworker w/ HTN presents to outside ED with primary complaint of not being able to breathe.
- 6 weeks of a dry cough, initially treated with Azithro
- Feeling short of breath, hard time working
- 5 weeks of fevers to 102F, drenching night sweats, lost 25 lbs
- Developed erythematous rash on lower extremities
- Legs became swollen
- Transferred to PPMC for critical care

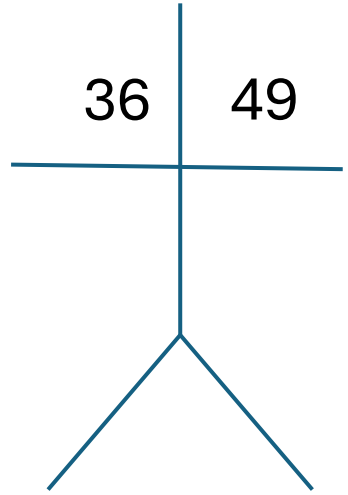
Case 6: P/E



- T 100F, HR 92, BP 146/82
- Appears tired, sitting in dark room
- HEENT: injected eyes, avoids light, erythematous, swollen gums
- Cardiac: RRR, 1/6 sys murmur
- Pulm: scattered crackles
- Skin: erythematous palpable purpura on lower extremities
- MSK: no sig tenderness/synovitis throughout

Case 6 data





Patient's values	Normal range
Urinalysis: 3+ RBCs, 100 WBCs, granular casts	
Kidney bx: focal and segmental necrotizing and crescentic glomerulonephritis, no complex deposition	
+ANA 1:160	< 1:80
+c-ANCA 1:160 +PR3 8	C-ANCA 1:20 +PR3 < 2 IU/mL

FUO: Granulomatosis with polyangiitis (GPA)

- 7.4% of autoimmune FUO cases *
- 55.3 % cases of GPA with fever **
- When to consider: (small vessel vasculitis)
  - Multi-system inflammation / ischemia
  - Weird ischemia
  - Pulmonary / renal syndrome
  - Systemic illness / FUO
- Diagnosis:
  - Evidence of small vessel vasculitis
  - Biopsy
  - Serologies: ANCA/MPO/PR3

*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
** Springer, JM et al. *J Med Internet Res,* 2020.

RHEUMATOLOGY made ridiculously simple™

Adam J. Brown, M.D.

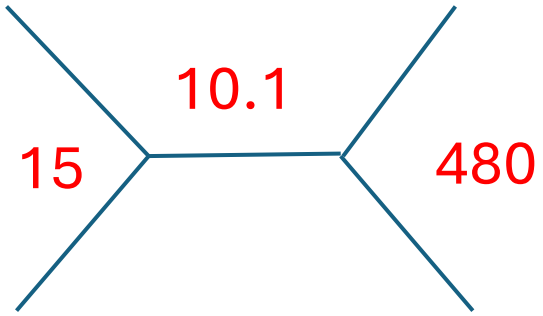
Case 7

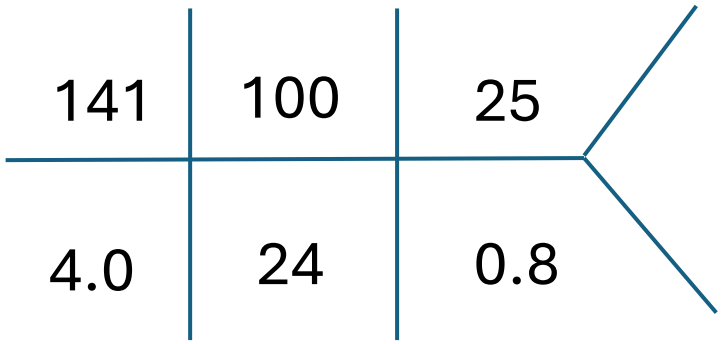
- 39 yo female, 7 months postpartum, presents to PCP due to 5.5 months of polyarticular inflammatory arthritis
- Unable to lift baby due to swollen hands
- Sleep disrupted by pain (and baby)
- Daily fevers ranging 99F-101F, lost 30 lbs
- Feeling short of breath, tired
- L eye has felt irritated, sensitive to light, red

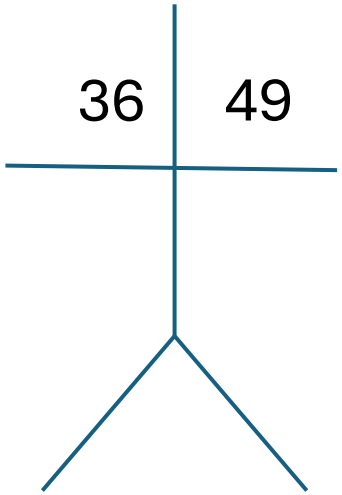
Case 7: P/E

- T 98F, HR 89, BP 110/89
- General: non-toxic, thin, tearful
- HEENT: moist mucous membranes, no ulcers, good dentition
- Cardiac: RRR, no m/r/g
- Pulm: no crackles, wheezes
- Skin: scaling rash on elbows
- MSK: tenderness/synovitis of PIPs, MCPs, wrists, elbows. Pain w/ b/l glenohumeral ROM and abduction. Small warm effusions in knees, ankles. Tenderness and synovitis of MTPs.

Case 7: data



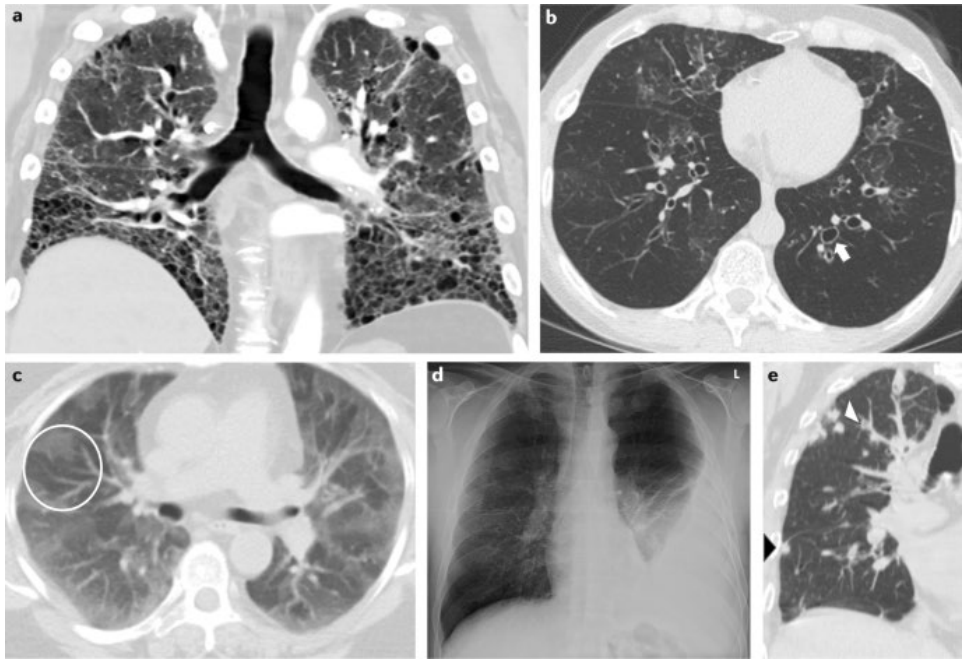




Patient's values	Normal range
+ANA 1:360	< 1:80
dsDNA 1 (-)ENA panel C3/C4 wnl	dsDNA < 10
ESR 86	< 20 mm/hr (women < 50 yo)
CRP 17	< 0.3 mg/dL
+RF 192	< 20 U/mL
+CCP > 250	< 20 U/mL

FUO: Rheumatoid Arthritis

- 3.52% of FUO autoimmune cases *
- 5.9 % of patients with RA who have fever
- Diagnosis:
  - Chronic polyarticular, symmetric inflammatory arthritis
  - Often proliferative, destructive
  - Systemic disease: eye, lung, inflammation
  - Serologies: RF / CCP (~80%)
- Fevers can occur prior to definitive diagnosis, during periods of active disease



* Betrains, A. et al. *Eur J Intern Med,* 2024 June.

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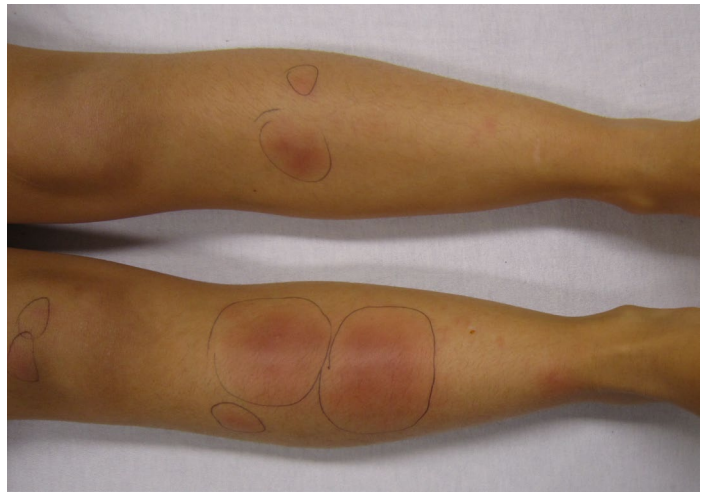
Case 8

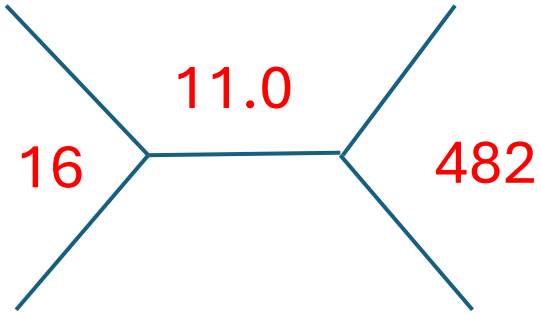
- 32 yo female presents to urgent care due to swollen ankles, painful rash, and fevers
- Fevers over past 2 weeks range 99-101F
- Has had trouble working as waitress because painful to walk
- Then lumps started to form on legs, a few on arms
- Ibuprofen helps a little

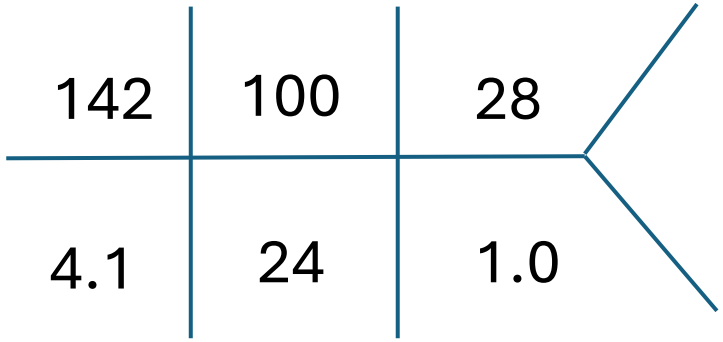
Case 8: P/E

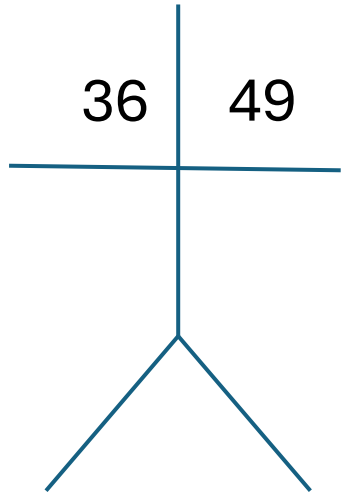
- T 99.8F, HR 101, BP 122/85
- General: non-toxic, appears tired, uncomfortable
- HEENT: no conjunctival injection, moist mucous membranes, no ulcers, good dentition
- Cardiac: mild tachycardia, reg rhythm, no m/r/g
- Pulm: no crackles, wheezes
- Skin: tender erythematous, warm nodules on lower extremities > upper extremities
- MSK: b/l ankles are warm, moderate effusions, decreased ROM in all planes

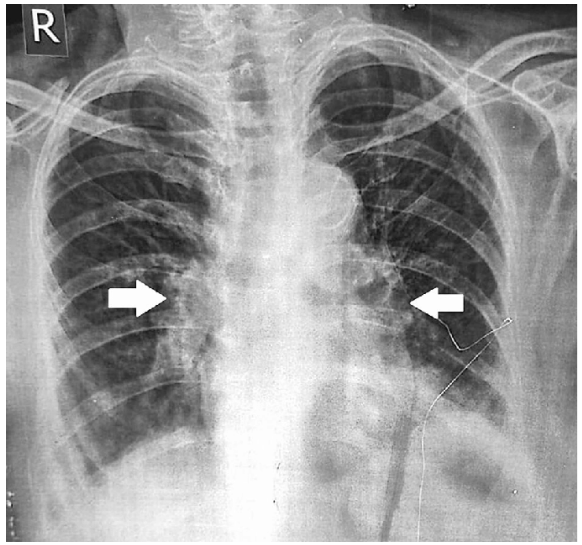


Case 8 data









Patient's values	Normal range
ESR 86	< 20 mm/hr (women < 50 yo)
CRP 17	< 0.3 mg/dL

FUO: Sarcoidosis

- 2 - 6 % of autoimmune FUO cases *
- 31 % of patients with sarcoidosis have fever **
- The great mimicker!
- Diagnosis:
  - Clinical: Lofgren's syndrome
  - Biopsy
  - ACE -- No! Not very helpful

*Mulders-Manders, CM, et al. *Best Pract & Research Clinical Rheum* 2016
*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022
** Behbehani, N. et al. *Respir Med*, 2007.

Rheumatologic causes of FUO: western vs non-western populations

Western populations

- Adult-Onset Still's Disease; 5% of all cases
- Large vessel vasculitis; 5%
- Systemic lupus erythematosus; 3%
- Sarcoidosis; 2%

Non-Western populations

- Adult-Onset Still's Disease; 2% of all cases
- Unclassified vasculitis; 2%
- Polymyalgia rheumatica; 2%
- Systemic lupus erythematosus; 2%

Mulders-Manders, CM, et al. *Best Pract & Research Clinical Rheum* 2016

Impact of a country's income

High income countries

- Significantly higher rheumatic disorders diagnosed in FUO (25.8%)
- Higher proportion of:
  - large vessel vasculitis (21.8%)
  - polymyalgia rheumatica (10.1%)
  - Behcet's disease (4.7%)
  - Sarcoidosis (6.3%)
  - Schnitzler syndrome (2.7%)
- Lower proportion of:
  - Adult onset Still's disease (17.2%)
  - Sjogren's syndrome (2.8%)

Low – middle income countries

- Significantly fewer rheumatic disorders diagnosed in FUO (19.8%)
- Lower proportion of:
  - large vessel vasculitis (10.6%)
  - polymyalgia rheumatica (5.3%)
  - Behcet's disease (2.5%)
  - Sarcoidosis (3.7%)
  - Schnitzler syndrome (1.6%)
- Higher proportion of:
  - Adult onset Still's disease (28.8%)
  - Sjogren's syndrome (4.5%)

Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022

And just for fun…

- Dr. Richie Wernick: “Google is a valid tool to use when a diagnosis is unknown”
- Me: “ChatGPT is a valid *tool* to use when a diagnosis is unknown”
  - Example: What is the ddx for a 21 year old female with fevers, dysphagia, inflammatory arthritis, and elevated inflammatory markers?
    - AOSD, SLE, rheumatic fever, Kawasaki disease, reactive arthritis, infectious etiologies (endocarditis, TB, disseminated fungal infx), viral syndromes.
    - Next steps in work-up: CBC, ESR, CRP, ANA, RF, anti-dsDNA, ferritin, ASO titers, blood cultures; echo, cxr, swabs/cultures, skin biopsy…
    - ?? Consult a rheumatologist??

Summary / closing thoughts

- Rule out infections and malignancy
- Longer duration of undiagnosed fever → more likely to be rheumatic etiology *
- May be diagnosis of exclusion
- Look for uncommon presentations of common diseases > uncommon diseases
- Objective data - tissue is the issue (but even this is flawed - ie mishandling sample, rhabdo affecting muscle biopsy, pathologist error, sampling error, etc), imaging, labs
- This is not a comprehensive list of all autoimmune causes of FUO
- Consider disease prevalence, availability of diagnostic techniques, diagnostic bias

*Betrains, A. et al. *Seminars in Arthritis and Rheumatism* 2022

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Questions?

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