CONSULT SERVICE *at* *the* MASSACHUSETTS GENERAL HOSPITAL

by a BWH fellow

41-year-old woman with subacute febrile illness and multisystem organ dysfunction

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Advances in Rheumatology

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Key learning point

- Key points: Describe the rheumatologic differential diagnosis for a systemically unwell patient with FUO and history of IVDU.
- Next best steps: Along with history and physical exam, perform extended social history, obtain laboratory testing based on patient interview testing that includes common drug related infections such as hepatitis serologies, HIV, blood cultures and infectious- or drug-related serum complements, cryoglobulins, and ANCA. If work up unrevealing, PET-CT can be helpful.

HPI

- 12/9: Initially presents to urgent care with fever to 102º, cough, sore throat, cough, DOE, and diarrhea. Reports last IVDU 4 weeks ago. COVID negative.

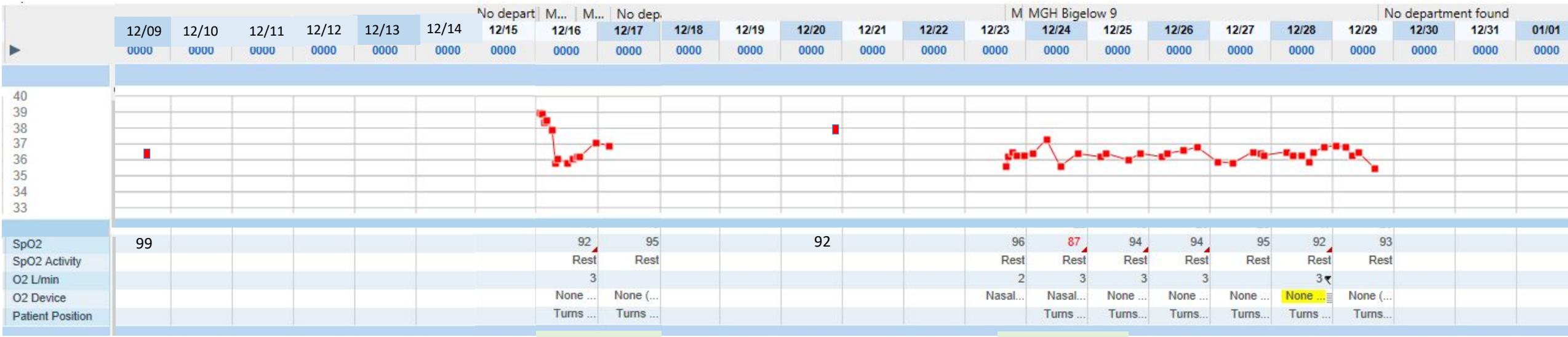
- 12/16: Returns to MGH ED with ongoing fevers to 102-104º, myalgias, worsening shortness of breath worse with exertion, abdominal pain, nausea and vomiting. Now reports relapse IV fentanyl 2 weeks ago.
  - Found to be pancytopenic with mild cholestatic liver injury.
  - Admitted but leaves AMA after ~24 hours when sister dies unexpectedly.

- 12/23-12/29: Represents to MGH ED with Tmax 104º at home, worsening nausea and vomiting.
  - Found to have new 2L O2 requirement, persistent pancytopenia, and worsening cholestatic liver injury.
  - Cross-sectional imaging reveals splenomegaly, abdominal lymphadenopathy and mild diffuse centrilobar GGOs.
  - Induced on suboxone but feels undertreated and leaves AMA despite diagnostic uncertainty.

HPI continued

- 1/18: Represents with 4 days of fevers, nausea and vomiting, LUQ pain, and weakness.
  - Admitted to MICU with hypoxemia and MAPs ~high 50s despite 3L volume resuscitation.
  - Course complicated by difficult balance between withdrawal symptoms and somnolence.

- 1/25: Rheumatology consulted. Complains of feeling fatigued but denies pain. Ongoing nausea and dyspnea on exertion.
  - Denies prior febrile episodes before 12/20. No arthralgias or rash including during febrile periods.
  - Pregnant 4 times with no miscarriages. No oral or vaginal ulcers. No alopecia, Raynaud's or photosensitivity. +Chronic dry mouth, no dry eyes.



Vancomycin

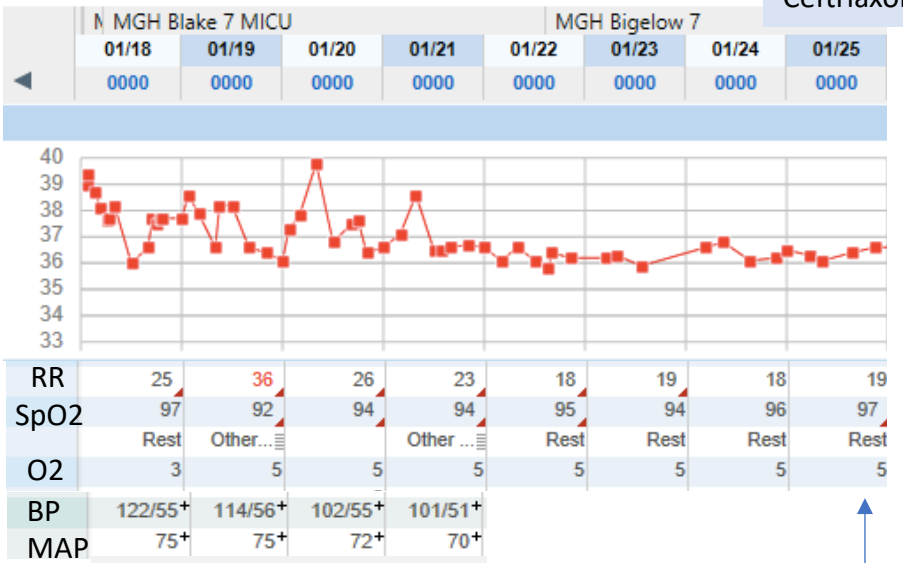
Ceftriaxone

Vancomycin

Ceftriaxone

Doxycycline

Furosemide



Norepinephrine

Vancomycin

Cefepime

Doxycycline

Rheumatology is consulted

PMH/ PSH

- Beta-thalassemia trait
- Borderline personality disorder diagnosed in childhood
- Victim of childhood physical abuse and adult sexual abuse
- Bipolar disorder diagnosed in adulthood
- Migraine HA
- Hepatitis C diagnosed 2012, spontaneously cleared 2013
- Cervical MSSA epidural abscess (2015) with C4-5 laminectomy and hardware
- Chronic neck pain and upper extremity weakness

Social history

- Longstanding polysubstance use disorder
  - Heroin use starting at age 16, dependence soon after; longest sobriety 4 years
  - Prior cocaine and alcohol requiring multiple detoxes, recently in remission
  - Daily cigarette use (1PPD) x 25 years
  - 6g IV fentanyl, 6 mg xanax
- Used same drug supplier for at least 2 years. Only uses tap water, never shares or licks needles but does reuse needles. Uses fresh cotton removed from new Q-tips. Stores drugs in dry area.

Social history continued

- 2 children age 1.5 and 8, currently in DCF care
- Undomiciled, currently living in hotel in Chelsea, occasionally with father of youngest child
- Last worked ~2 years ago as a fundraiser for the Democratic party
- Prior incarceration, dates unknown
- Has never travelled outside of New England
- No pets

Medications

- Clonidine 0.3 mg TID
- Lurasidone 40 mg qAM
- Sertraline 100 mg qAM
- Zolpidem 5 mg qHS PRN
- Topiramate 25 mg BID
- Lamotrigine 25 mg qDay
- Suboxone 8 mg BID
- Gabapentin 1200 mg BID

No known drug allergies

No recent medications changes or supplements

Family history

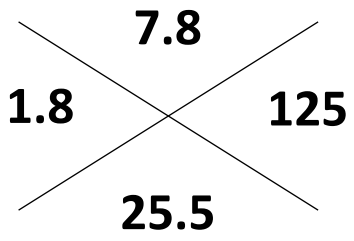
- Does not know ancestry but identifies as white
- Mother: bipolar disorder, IV drug abuse, lung cancer, dementia
- Maternal grandmother: Schizophrenia
- Maternal aunts (2): Breast cancer in mid-40s
- Son: ADD

No FH autoimmune disease

Physical Exam

- BP 111/54 | Pulse 68 | Temp 36.3 °C | Resp 20 | **SpO2 96% on 5L** | BMI 27.93 kg/m²
- Gen: **Chronically ill appearing, lying in bed wearing O2 i**n NAD
- HEENT: **Temporal wasting.** PERRL, EOMI, MMM with normal salivary pool, oropharynx pink without ulcerations. No conjunctival erythema. No salivary gland enlargement.
- Chest: **Bibasilar crackles**
- CV: RRR, no murmurs
- Abd: soft, non-tender, **distended with hepatomegaly and splenomegaly**, no fluid wave
- Extremities: **1+ bilateral LEE,** 2+ radial and pedal pulses. **Thin arms with muscle wasting.**
- Neuro: Somnolence limits participation in exam. No rigidity. Brisk reflexes throughout, 5 beats clonus bilaterally.
- Skin: **Tattoo L upper arm appears normal without hypertrophic changes. Track marks upper extremities and hands.** No alopecia, nail change, rashes, bruising, petechiae, telangiectasias, tophi, appreciable calcinosis, or nodules.
- Musculoskeletal Examination: No deformity, erythema, warmth, swelling, effusion, tenderness, limited ROM throughout.

12/16



MCV 54

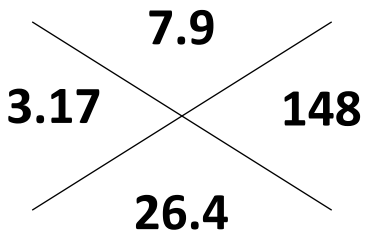
Normal diff

131	103	16	101
4.2	**20**	0.95	

ALT 54
AST 100
AlkP 351
Tbili 0.5
D bili <0.2
Alb 3.5
TP 7.9

ESR NA
CRP NA
Ferritin NA
LDH 272
D-dimer 1973
Haptoglobin 20
UA: bland

12/23



MCV 54

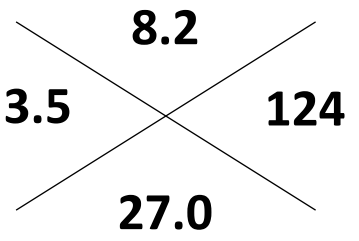
Normal diff

135	105	10	101
3.9	23	0.8	

ALT 46
AST 108
AlkP 468
Tbili 0.5
D bili <0.2
Alb 3.3
TP 6.3

ESR 22
CRP 22.8
Ferritin 53
LDH 277
D-dimer 1184
Haptoglobin <10
UA: bland

1/18



MCV 55.7

83.9 PMN, 12.6% lymphs

132	103	18	102
3.6	**20**	0.85	

ALT 67
AST 115
AlkP 784
Tbili 2.2
D bili 1.6
Alb 3.1
TP 6.7

ESR 20
CRP 133
Ferritin 163
LDH 271
Fibrinogen 230
Haptoglobin <10
UA: bland

Immune:
ANA 1:160, speckled; dsDNA negative, Sm, RNP negative **Ro + 52.51**, La negative
C3 90, C4 33
AMA, LMK-1 negative
RF, CCP, ANCA negative
IgG 1627; IgA 382; IgM 1027
0.29 IgG K M spike; 0.27 IgG L M spike;
K/L FLC 46/ 63, no Bence Jones protein

Utox:
+Fentanyl, norfentanyl, methadone
Negative amphetamine, cocaine, phencyclidine, THC

Blood cx
- 12/16, 12/21, 12/23, 1/18 NG x 7 days

Urine:
- 12/24 GC/CT urine NAAT: Neg
- 1/18: Abundant Garderella vaginalis

Respiratory:
- COVID neg: 12/9, 12/16, 12/20, 12/23, 1/18, 1/19
- 2/16 Urine legionella: Neg
- 1/21 Sputum culture: Few yeast

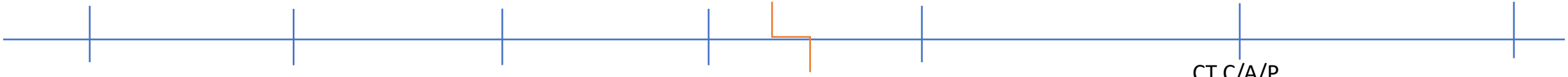
Serologies/PCRs/Ags:

12/16
- EBNA IgG, VCA IgG positive, CMV IgM positive

12/23
- CMV PCR neg
- HIV AB/Ag neg, PCR neg
- Lyme Ab neg, Anaplasma/Erlichia PCR neg, Babesia smear neg
- Toxo IgG neg**, Toxo IgM positive**
- **HCV Ab positive,** HCV PCR negative
- HAV/HBV non-immune
- **Parvo IgG Pos**, IgM Neg

1/18
- Toxo IgG Neg, **IgM Pos**
- CMV IgG: Positive, CMV IgM Positive
- Adenovirus PCR: Negative
- Tspot: Negative
- Covid Abs: Negative

A brief detour through prior imaging



1/16 — CT PE:

Prominent bilateral hilar nodes 1.0 cm L, 0.8 cm R

Multiple small scattered pulmonary nodules

Mild centrilobar and paraseptal emphysema

No PE, PA 2.9 cm

2/17 — CT Chest:

Stable unchanged hilar adenopathy, pulmonary nodules, and mild emphysema

PA 3.1 cm

1/19 — CT PE (28wga):

New LUL patchy GGO, mild cardiomegaly, mild splenomegaly 14.2 cm

PA 3.5 cm

Stable unchanged hilar adenopathy, pulmonary nodules, and mild emphysema

9/19 — CTAP:

Splenomegaly 14 cm

New prominent RP lymph nodes

12/16/20 — CT PE:

Dependent GGO in upper and lower lobes

Enlarged celiac axis LN

Stable unchanged hilar adenopathy, pulmonary nodules, and mild emphysema.

No PE, PA 3.5 cm

12/24/20 — CT C/A/P

New mild septal thickening and bronchial wall thickening. Mild diffuse centrilobular GGO. Atypical for COVID PNA.

Slight increased bilateral hilar lymphadenopathy

Spleen 17.6 cm
Upper abdominal periportal and peripancreatic LAD

TTE:
LA dilation.
Mild-moderate MR.
Focal thickening of the non coronary leaflet of the aortic valve with a trivial mobile echodensity on the leaflet tip

1/18/21 — CT PE

New scattered bilateral pulmonary nodule ≤ 6 mm

Stable bilateral hilar and abdominal adenopathy and spenomegaly

No PE, PA 3.5 cm

TTE:
Previously noted AV mobile thickening not noted

41 y/o woman with recent relapse of IVDU re-admitted with subacute FUO of 7-8 weeks and multisystem organ dysfunction characterized by 1) *pancytopenia with intravascular hemolysis; 2)hypoxemia with diffuse pulmonary ground glass opacities; 3) cholestatic liver injury; 4) massive hepatosplenomegaly and lymphadenopathy; 5) shock, now resolved.*

FUO

FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

ROBERT G. PETERSDORF* AND PAUL B. BEESON

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

- Prospective study of 100 patients initiated in 1952

In an attempt to avoid some of the drawbacks just cited, and to obtain a present-day sampling of the problem of unexplained fever in adults, we undertook the present study in 1952. It was decided simply to note cases of prolonged unexplained fever satisfying certain criteria, at the time of their occurrence, with the intention of further study by follow-up methods at a later date. The criteria selected were: *Illness of more than three weeks' duration*. This tended to eliminate the acute self-limited infectious diseases. In some reported series such cases have comprised as much as half of the case material. *Fever higher than 101°F on several occasions*. This eliminated the entity of 'habitual hyperthermia' (3). *Diagnosis uncertain after one week of study in hospital*. This time interval was selected as that which allows completion of the usual laboratory studies made initially in attempts to identify the cause of a febrile illness, examples being bacteriologic and serologic tests, radiologic examinations, skin tests, etc.

FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

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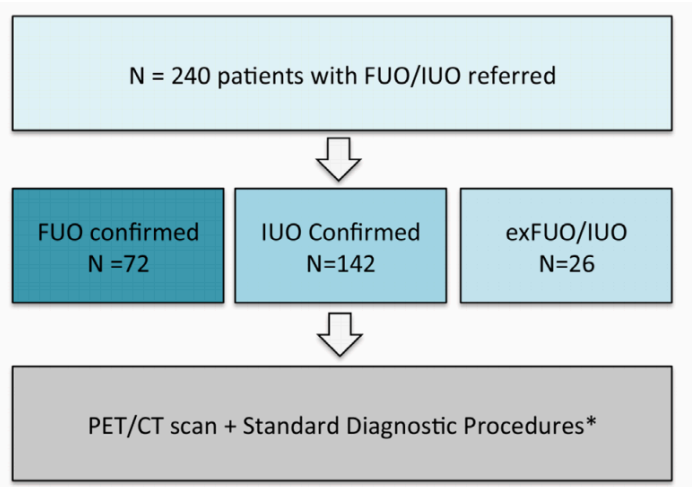
TABLE I

Diagnostic Categories of the 100 Cases

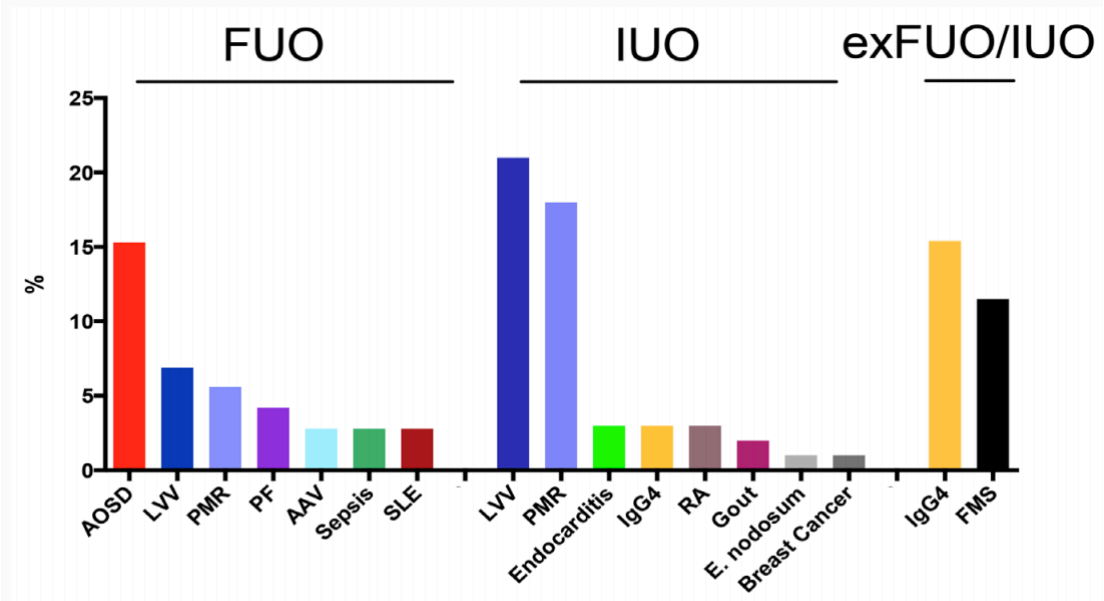
Category	Number of Cases	
Infections		
Tuberculosis	11	
Liver and biliary tract infections	7	
Bacterial endocarditis	5	
Abdominal abscess	4	
Pyelonephritis	3	
Psittacosis	2	
Brucellosis	1	
Cirrhosis with E. coli bacteremia	1	
Gonococcal arthritis	1	
Malaria	1	
Total		36
Neoplastic diseases		
Disseminated carcinomatosis	7	
Localized tumor	2	
Lymphomas and leukemias	8	
No histologic diagnosis made	2	
		19
Collagen disease		
Rheumatic fever	6	
Systemic lupus erythematosus	5	
Unclassified	2	
		13
Pulmonary embolization		
Following myocardial infarction	1	
Endocardial fibroelastosis	1	
Thrombophlebitis migrans	1	
		3
Benign non-specific pericarditis		2
Sarcoidosis		2
Hypersensitivity states		
Granulomatous hepatitis	2	
Erythema multiforme	1	
Drug fever (dilantin)	1	
		4
Cranial arteritis		2
Periodic disease		5
Miscellaneous diseases		
Weber-Christian disease	1	
Thyroiditis	1	
Rupture of the spleen and pancreatitis	1	
Myelofibrosis	1	
		4
Factitious fever		3
No diagnosis made		7
Total		100

Prospective Study of PET-CT in FUO



CRP >30
ESR > age adjusted

Symptoms resolved



Final diagnosis was established in 190 patients (79.2 %)

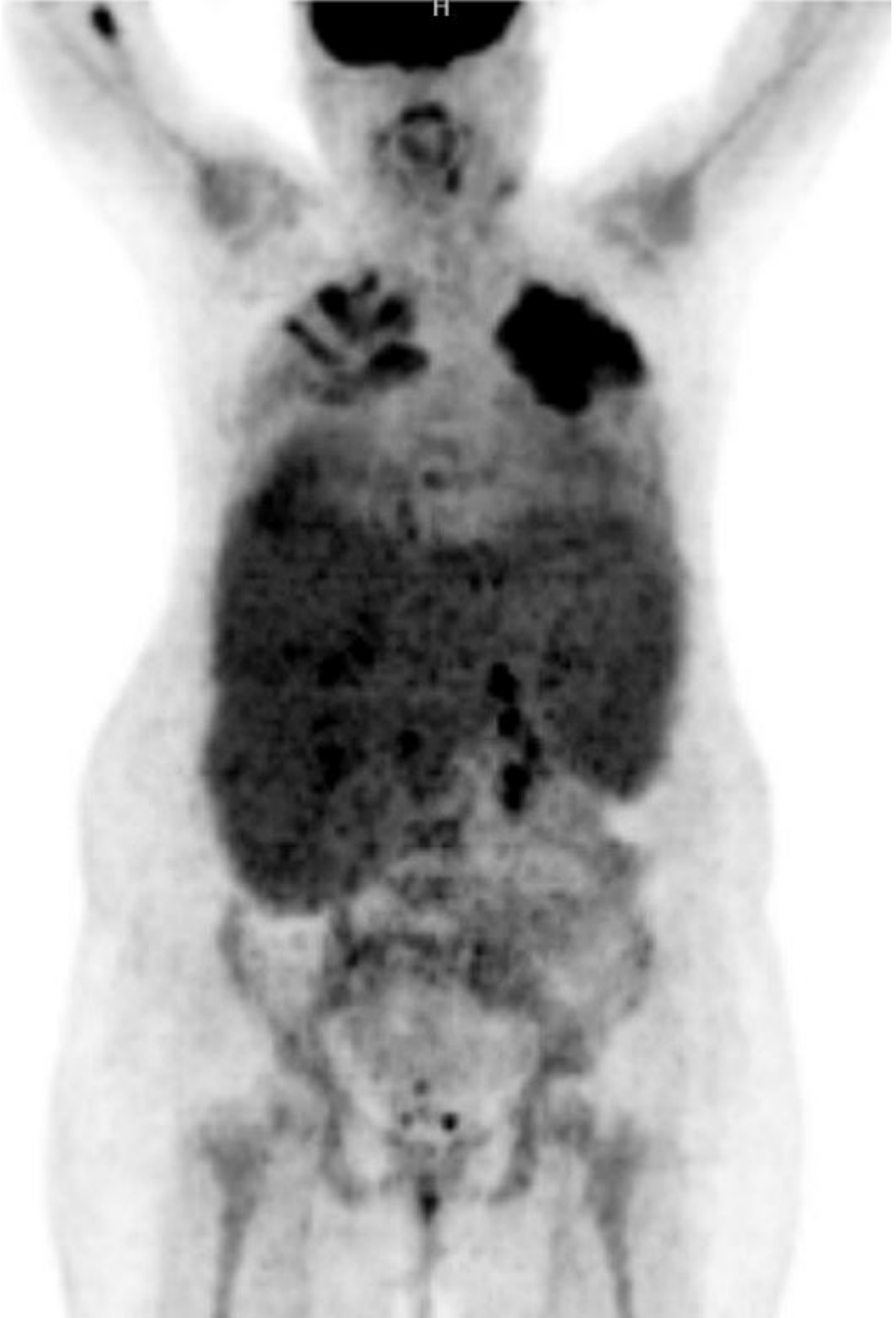
PET-CT helpful in 56.7% patients
Sensitivity: 91.1
Specificity: 21.7 **

**BM/LN uptake classified negative,
Specificity increases to 53.8%

PPV 76%
NPV 80.6%
Diagnostic accuracy: 77%

Schönau V, *et al*. *Ann Rheum Dis* 2018;**77**:70–77. doi:10.1136/annrheumdis-2017-211687

BMJ



PET-CT 1/21:

Moderately intense FDG uptake in the lungs with underlying GGOs.

Diffusely prominent but nonfocal uptake with hepatosplenomegaly and low level uptake in hilar and upper abdominal lymph nodes. More intense uptake at periportal lymph nodes.

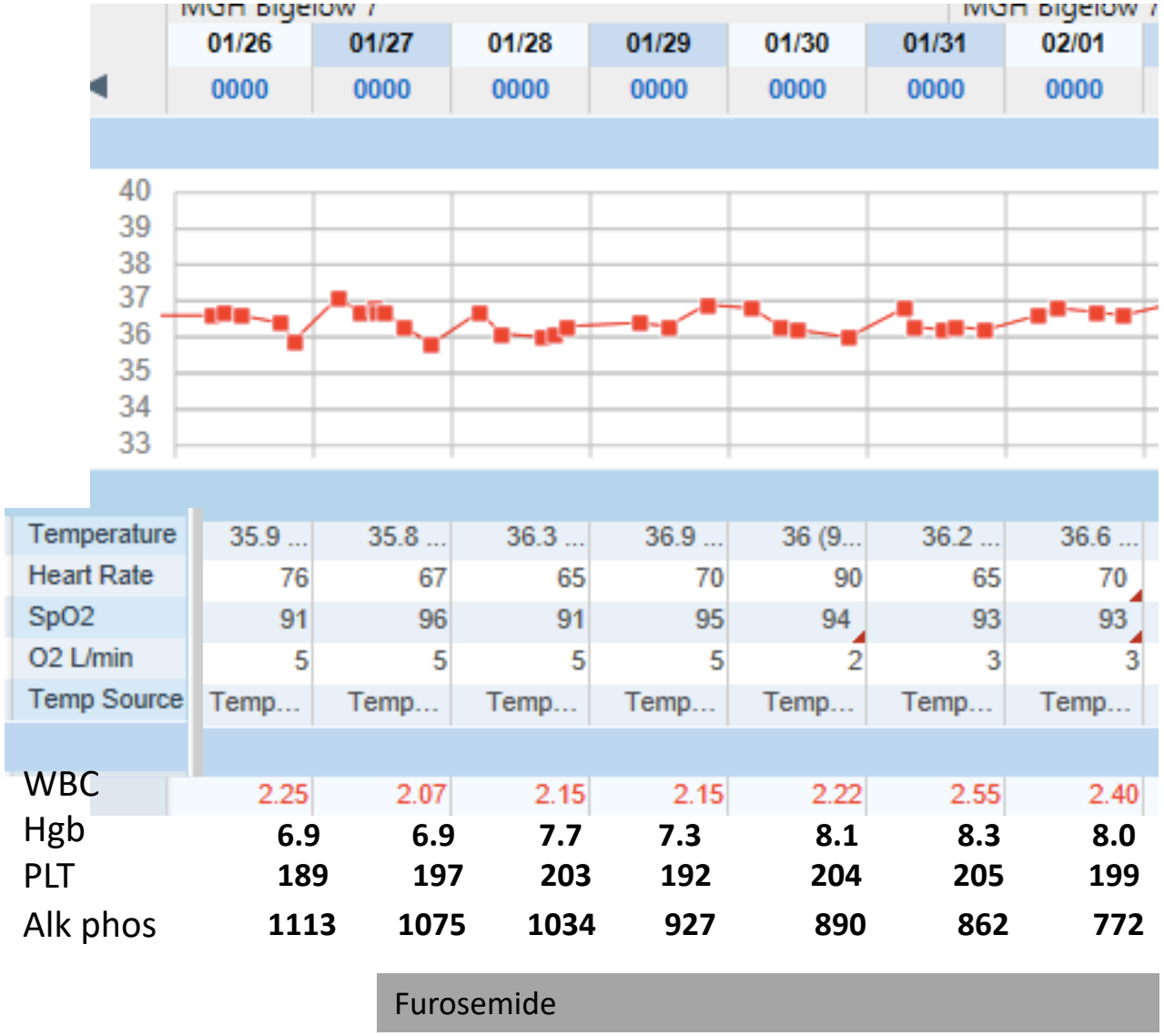
Peripheral flow 12/26 and 1/18 unremarkable.

Periportal lymph node biopsy 1/23:

Slight reactive lymphoid hyperplasia.

Note: The specimen consists of cores of lymph node with scattered primary follicles and few follicles with small germinal centers. Also present are interfollicular plasma cells, patent sinuses and clusters of histiocytes with anthracosis.

HHV8 staining is negative. In-situ hybridization for Epstein-Barr virus encoded RNA (EBER) is negative. There is no evidence of lymphoma or other neoplasm.

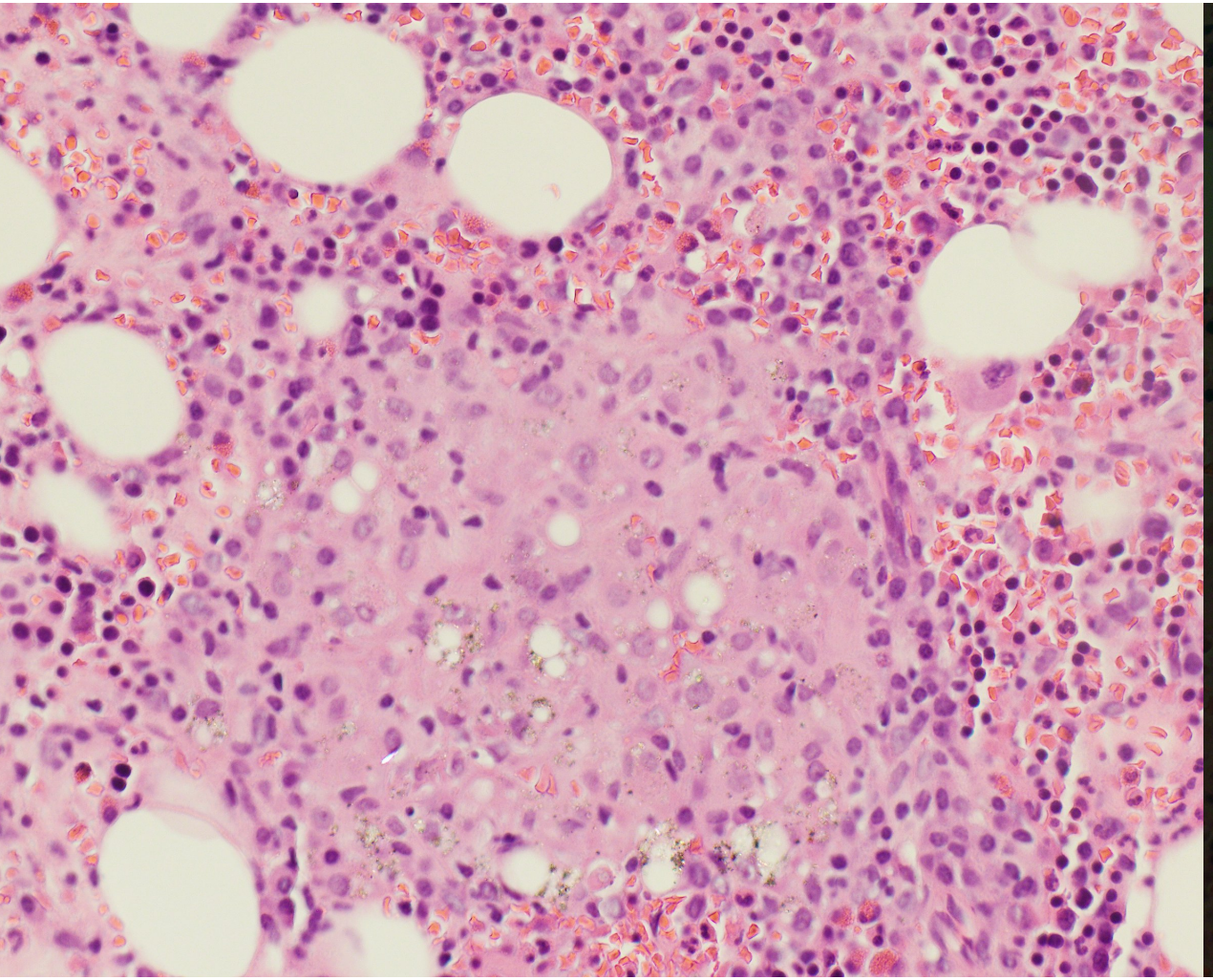


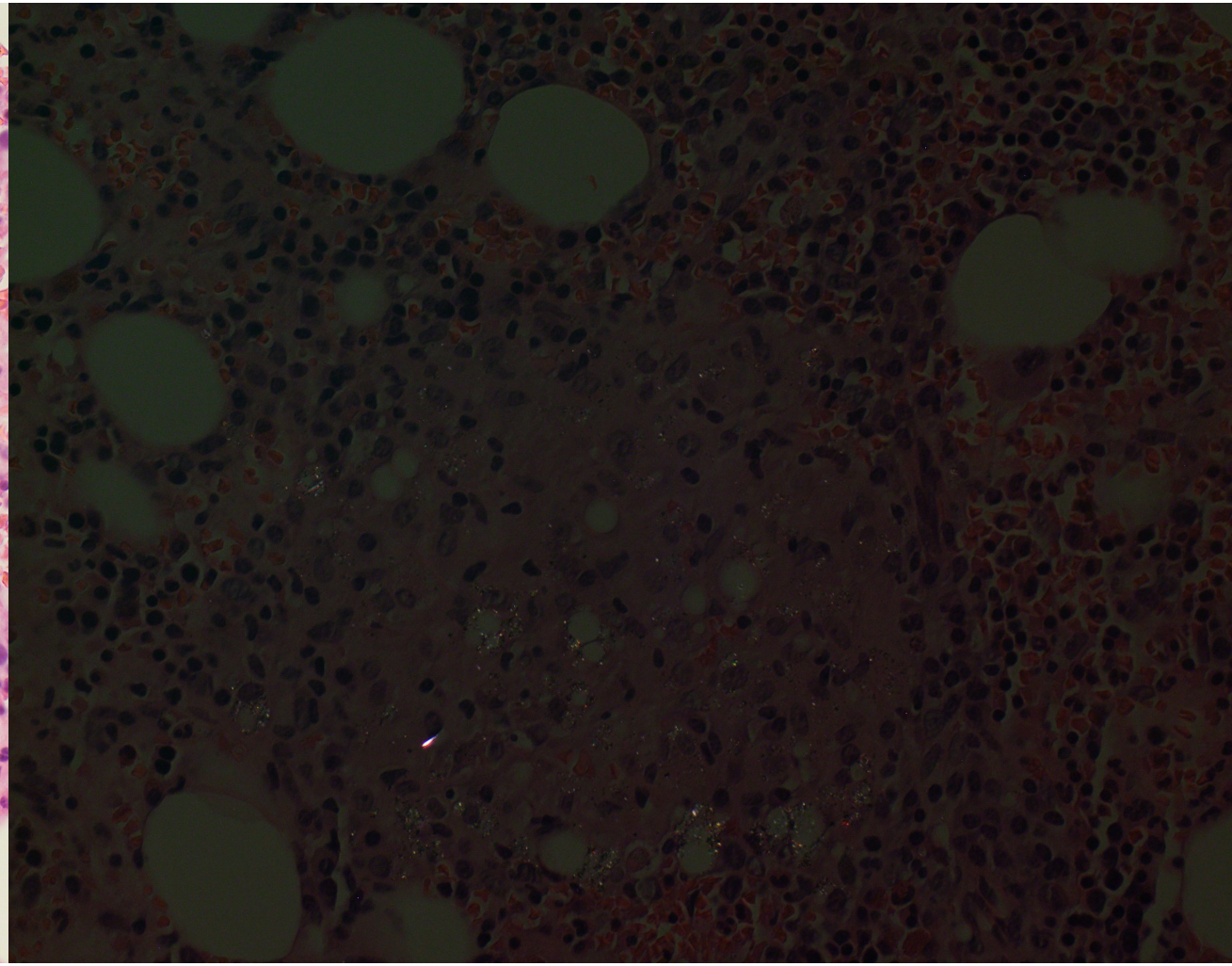
ACE 104 (ULN 80)
25-OH Vit D 8
1-25 OH VitD 20 (18-78)
NL urinary calcium

CRP 3.1
Haptoglobin <8
ACL IgM 37, LAC and B2GP negative

Cryoglobulins: <1%, Monoclonal IgM x2 Polyclonal IgG

A diagnostic test is performed





Normocellular marrow with maturing trilineage hematopoiesis and granulomatous inflammation associated with polarizing crystalline material.

**Has never been reported before in bone marrow

Talc granulomatosis: A sarcoidosis mimic

- Occurs in IV drug uses, most commonly associated with crushed pills
- Symptoms range from asymptomatic to exertional dyspnea to systemic illness with B symptoms
- Chest CT can show diffuse small pulmonary nodules, ground-glass opacities, and emphysema. Late finding of fibrosis.
- Lung biopsies show talc crystals lodge in pulmonary vascular bed with initial neutrophilic arteritis then granulomatous inflammation.
- Pulmonary artery involvement causes pHTN while interstitial disease leads to hypoxia with increased A-a gradient.
- Treatment is removal of exposure

Case follow up

- Endorses worsening HA - gets bMRI while admitted – unremarkable
- Cardiac MRI nondiagnostic due to lack of late gadolinium images
- Referred to MEEI for complete retinal and visual field exam
- Hospital day 16, requests discharge due to planned DCF visit with children
- Discharged with rapid rheumatology and pulmonary follow up, plan for repeat chest CT and PFTs
- Unfortunately, no-showed all follow up appointments
- Re-admitted 7/19-7/30 with fevers, shock, and ongoing pancytopenia. found to have high grade polymicrobial bacteremia (MSSA of 2 types, Enterobacter chloachea, Strep mitis) from presumed endocarditis. Discharged with 6-week course of antibiotics.

What can a rheumatologist add to the evaluation of patient with IVDU and fever?

- Diagnose drug-related vasculitis, including talc granulomatosis!