A 54M with recurrent infections presents with ongoing neutropenia and splenomegaly

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LEARNING OBJECTIVE

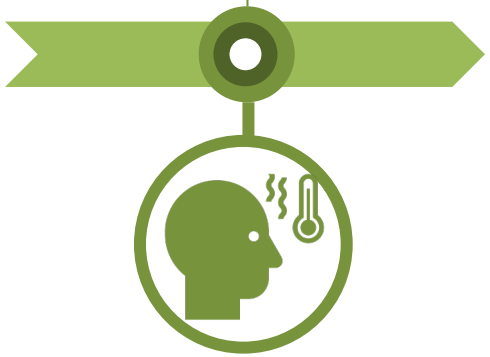
- Review hematologic manifestations seen in rheumatoid arthritis
  - Describe the typical clinical presentations
  - Review associated treatment strategies

Next Best Steps:

- Identify risk factors for hematologic complications in rheumatoid arthritis

HISTORY OF PRESENTING ILLNESS

<u>2 months prior</u>:
Develops 'hemorrhoid pain' that progressed to involve scrotum

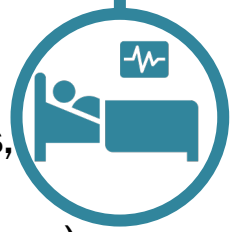


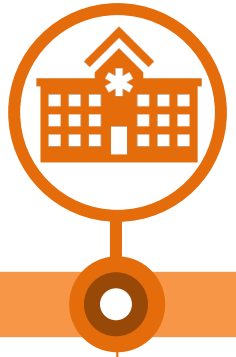
Lactate 4.1, WBC 4.2

Debridement of L gluteal abscess, necrotic scrotal tissue
(Bacteroides, Clostridium, Group A Strep)

Repeat debridements (x4) of scrotal soft tissues, perineal skin, L gluteus

Given ertapenem





Discharged to rehab

Ongoing leukopenia (WBC 1.5-3)

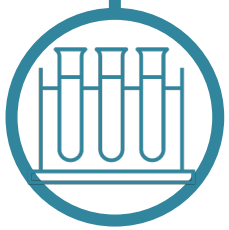
HOSPITAL COURSE

Current Admission:
New onset of acute abdominal pain at rehab

RUQ tenderness in the ED

CTAP with acute cholecystitis and massive splenomegaly.
Ongoing leukopenia -> cholecystostomy tube

Hematology Consult:
Leukopenia due to ertapenem?
Given G-CSF
Negative workup, but:
ANA 1:640, RF 377, CCP >340



Rheumatology consult

Felty syndrome?

ADDITIONAL HISTORY

- One day of L dorsal hand and wrist pain with difficulty making a fist. No swollen/red joints.

- ROS:
  - +35lb weight loss since illness
  - +fatigue
  - +malaise
  - +dry cough (attributes to cigarettes)
  - +abdominal pain at CCY tube site
  - +redness of face and neck after sun

  - Joint swelling
  - Fevers, chills, night sweats
  - Anorexia
  - Chest pain
  - Nausea, vomiting, diarrhea
  - Dysuria
  - Alopecia, mucosal ulcerations

PAST MEDICAL HISTORY

PAST MEDICAL HISTORY

- Fournier's gangrene (necrotic soft tissue infection of scrotum and perineum)
- Splenomegaly
- Neutropenia
- Prediabetes

SOCIAL HISTORY

- Lives in Quincy, MA.
- Not working, used to do deliveries
- Tobacco: 3/4ppd for >30 years
- Alcohol: 2-3 drinks/month
- Illicits: denies

MEDICATIONS

- Clindamycin 300mg tid
- Dilaudid 4mg q3h PRN (postoperative)
- Ibuprofen 200mg PRN
- Metformin 1000mg bid
- Nystatin cream topical

FAMILY HISTORY

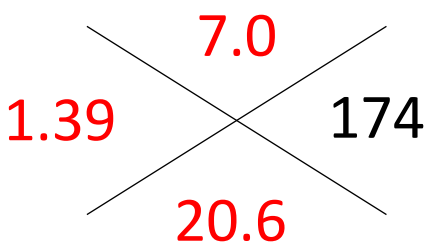
- No family history of autoimmune disease
- Mother: diverticulitis
- Father: T2DM
- Brother: deceased from ALS

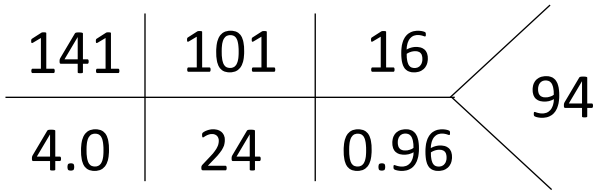
PHYSICAL EXAMINATION

T 36.9 | HR 101 | BP 85/50 | RR 18 | SpO2 98% (RA) | BMI 24.8

- Gen: lying in bed, in NAD
- CV: RRR, no murmurs/rubs/gallops
- Pulm: normal respiratory effort on RA, clear bilaterally
- Abd: percutaneous CCY in RUQ c/d/i, no tenderness to palpation; splenomegaly to L pelvic brim
- Ext: WWP, mild clubbing of fingers, no edema; multiple healed surgical scars in groin
- MSK: pain active ROM of L wrist with L 3rd PIP tenderness and pain with finger flexion; no deformities noted; no tenderness or pain in R hand, no elbow, MTP, ankle, knee tenderness, swelling or warmth

LABORATORY EVALUATION





AST 9

ALT 11

AlkP 104

Tbili 1.2 (Dbili 0.3)

TP 7.9

Alb 3.7

Abs Neut: 0.60

Monos 16%

Bands 4%

Myelocytes 3%

Metamyelocytes 1%

LDH 145

PT/PTT normal

ANA 1:640 diffuse

dsDNA, Ro, La, Sm, RNP negative; C3/C4 normal

RF 377, CCP >340

CPK 16

Ferritin 362

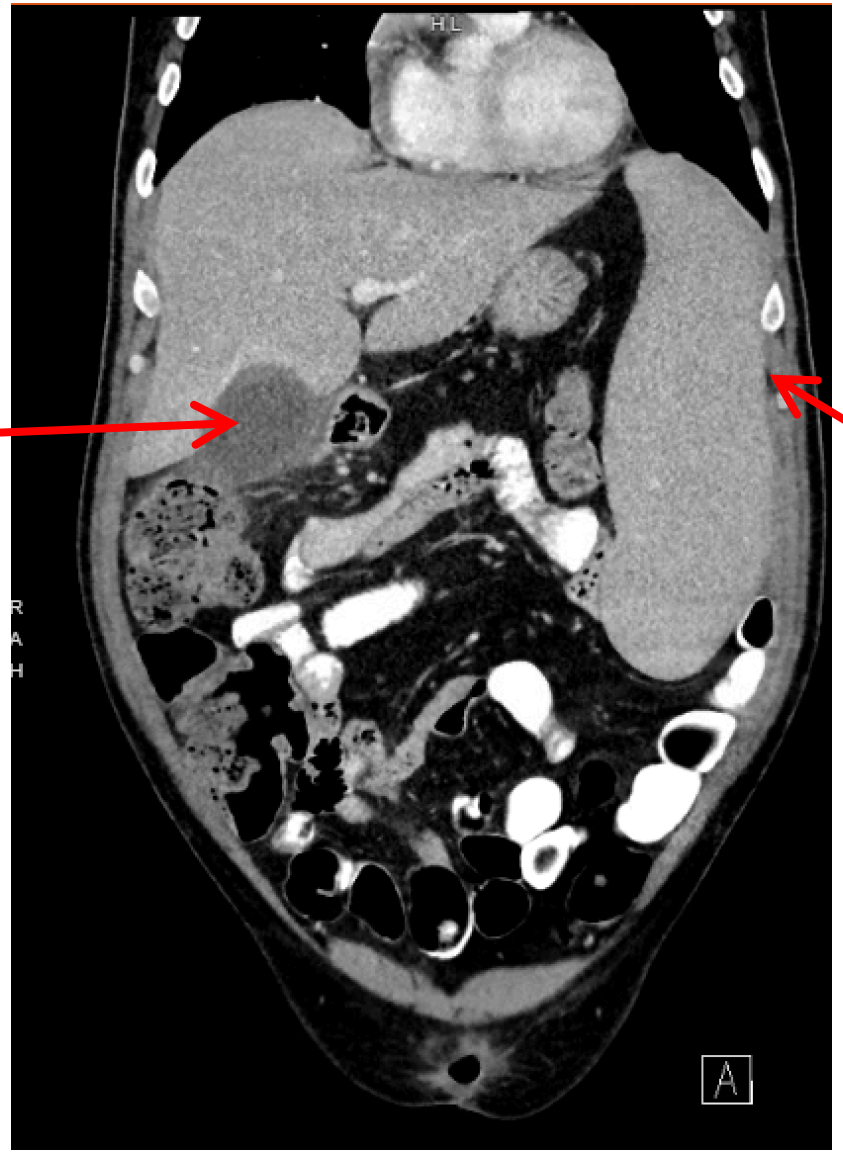
B12 839, Folate 18.1, Zinc 0.71

CRP 119, ESR 86

NEGATIVE INFECTIOUS STUDIES

- B-D glucan
- HIV
- HTLV
- EBV
- Parvovirus B19
- Strongyloides
- HAV, HBV, HCV

CT ABDOMEN/PELVIS



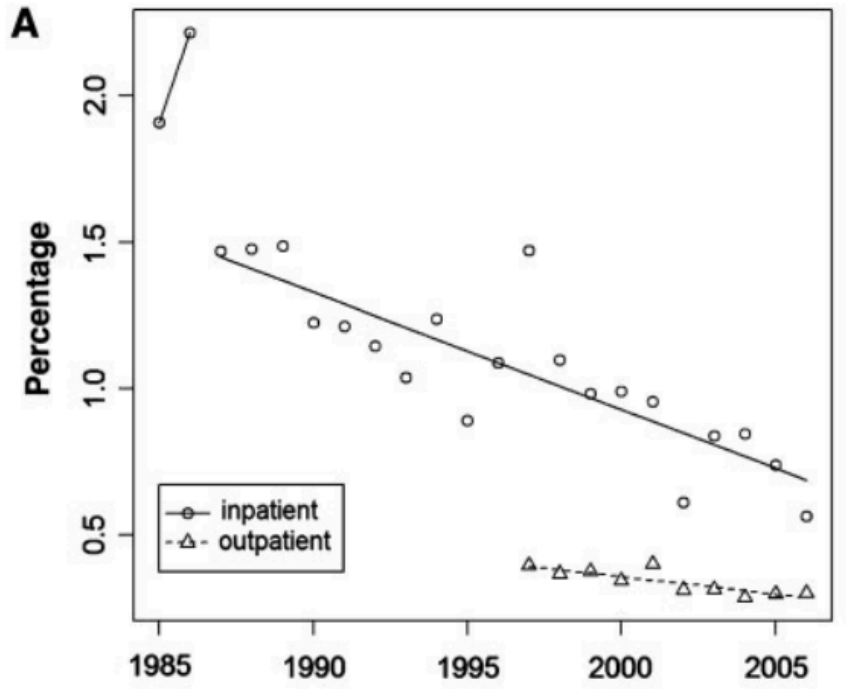
DETOUR!

Felty Syndrome

LGL Leukemia

WHAT IS FELTY SYNDROME?

- Combination of RA, splenomegaly, and neutropenia
- First described in 1924
- Occurs in <1% of RA patients with declining prevalence
  - LGL Leukemia defined 1985 (reclassification)
  - Methotrexate?



THE NEW ENGLAND JOURNAL OF MEDICINE March 28, 1985

EFFICACY OF LOW-DOSE METHOTREXATE IN RHEUMATOID ARTHRITIS

MICHAEL E. WEINBLATT, M.D., JONATHAN S. COBLYN, M.D., DAVID A. FOX, M.D., PATRICIA A. FRASER, M.D., DONALD E. HOLDSWORTH, M.D., DAVID N. GLASS, M.B., CH.B., AND DAVID E. TRENTHAM, M.D.

Bartels, J Rheum, 2010.

FELTY SYNDROME PRESENTATION

- Typically described with long-standing, erosive, seropositive disease
  - Up to 1/3 do not have active synovitis, though elevated ESR is usually seen
  - Case reports of non-articular or pre-articular Felty's syndrome
- Average age = 60
- 2-3:1 F:M ratio
- More likely to have other extraarticular manifestations
  - Vasculitis skin lesions (16-41%)
  - Mononeuritis multiplex (14-24%)
  - Rheumatoid nodules (53-82%)
  - Episcleritis (3-11%)

Campion, Medicine, 1990

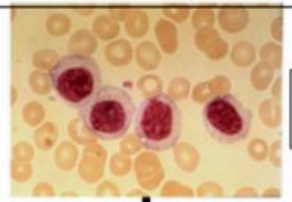
LGL LEUKEMIA IN RA

- LGL = Large Granular Lymphocytes
  - Subset of lymphoid cells, normal = 10-15% of PBMCs with two major lineages:
    - CD3+ T-cells
    - CD3- NK LGL
  - Clonal expansion = LGL Leukemia
    - T-cell LGL Leukemia (85% of LGL leukemia) -> associated with STAT3 mutation
    - NK LGL (15% of LGL leukemia)
- Typically presents with neutropenia and splenomegaly
  - ~20% of T-LGL patients have RA
- 85-90% of patients with FS and LGL leukemia have HLA-DR4 – suggests a similar/common immunologic mechanism -> may be part of spectrum

Liu Curr Opin Heme, 2010.

Clinical context: neutropenia, recurrent infections, anemia, autoimmune conditions, rheumatoid arthritis, lymphocytosis

Blood smear: excess of large granular lymphocytes?



yes

Flow cytometry analysis using CD3/5/4/8/16/56/57, TCRγ rearrangement,
(Stat 3 mutation, Vβ repertoire and KIR phenotyping, not routinely done as this stage)

Polyclonal

Reactive LGL proliferation

- Post-splenectomy, viral infection (CMV, HIV, EBV)
- Bone marrow/organ transplantation,...

GREY ZONE

- Low LGL count around 0.5-1 x 10.9/L, and clonal evidence
- Pancytopenia, lymphopenia, with clinical evocative context

Bone marrow biopsy + Immunohistochemistry

- Interstitial and intravascular subtle LGL
- Infiltration of clusters of CD3+/CD8+/GzB+/TiA1+ LGL
- Lymphoid nodules of B and T CD4 cells

yes

True clonal LGL expansion

T or NK LGL Leukemia
Clonal TCRγ

Additional tests (if required)

- Stat3/5b/NFKB...mutation
- Vβ repertoire, KIR phenotyping

Gazitt, *Hematology Am Soc Hematol , 2017*

TREATMENT

- Felty's syndrome
  - Treatment of underlying RA – MTX, rituximab, other DMARDs
  - G-CSF support
  - Splenectomy in refractory cases

- LGL Leukemia
  - Methotrexate, Cyclophosphamide, Cyclosporine
  - Splenectomy in refractory cases

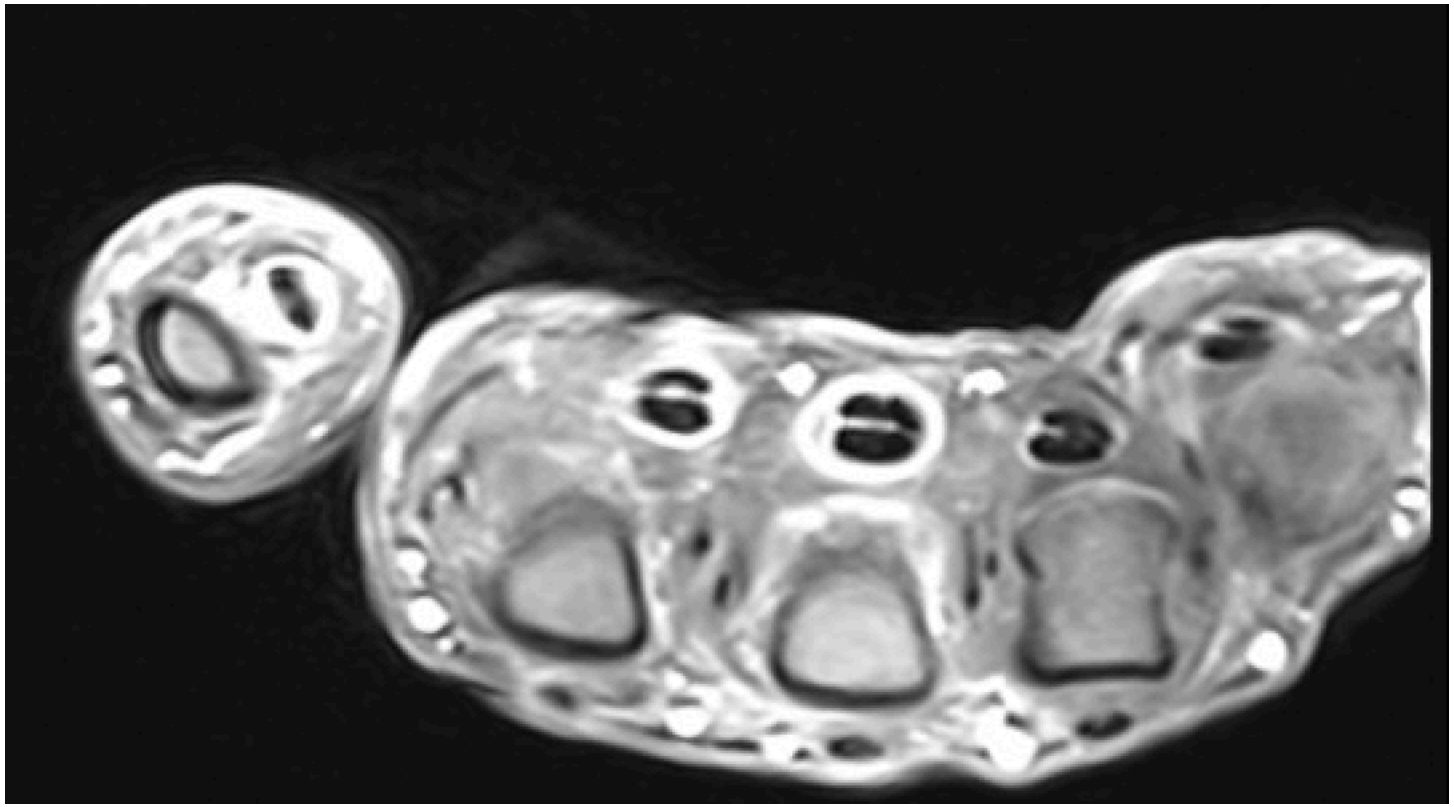
Liu Curr Opin Heme, 2010.

BACK TO OUR PATIENT …

- No significant peripheral LGLs
- Rapid Heme Panel negative for STAT3, IKZF1, ERG, KMT2A-PTD, FLT3-ITD
- Normal Peripheral Flow Cytometry with 2% LGL
- Bone marrow biopsy – suboptimal sample, moderate hypercellularity, no blasts. No flow cytometry abnormalities with LGL 5%

= NOT LGL Leukemia

MRI L HAND



Impression

1. Diffuse left hand enhancing flexor tenosynovitis and mild third MCP synovial enhancement is in keeping with inflammatory arthritis. No erosions.
2. Mild flexor pollicis longus tendinosis. No tendon tear.

SUMMARY

54M with recurrent infections (SSTI, cholecystitis), splenomegaly, neutropenia. Found to have positive RF, CCP with one day of L hand pain (tenosynovitis and synovitis on MRI) and no evidence of LGL leukemia

- Are we confident calling this Felty's syndrome?
- Next steps?

FOLLOW UP

- Discussed with hematology -> as we did not think definitely Felty's syndrome, they remained concerned about splenic lymphoma
- Proceed with splenectomy (+ cholecystectomy)

- Final pathology = expanded clonal population of gamma/delta T-cells
  - Low proliferation index and no cytologic atypia
  - Ultimately = low grade gamma/delta T-cell lymphoma

Human Pathology (2017) 66, 216–221

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Case study

Florid splenic γ/δ T-cell proliferation in patients with splenomegaly and cytopenias: a "high stakes" diagnostic challenge

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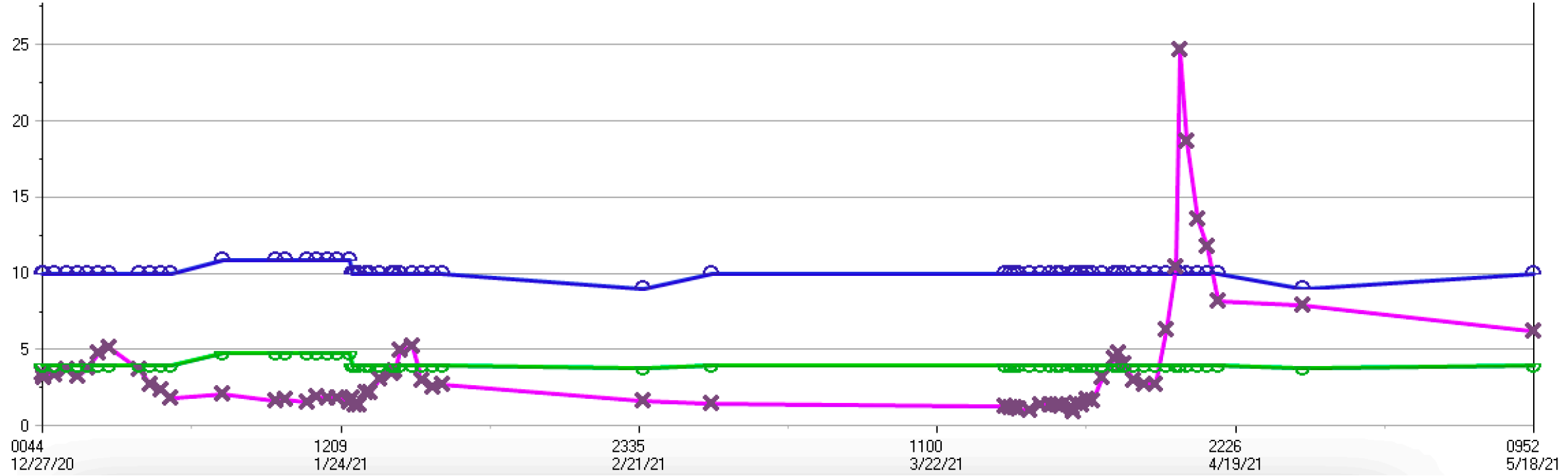
[b] *Department of Pathology and Laboratory Medicine, Penn State Hershey Medical Center, Hershey, PA 17033*

2 cases of low-grade gamma/delta T-cell proliferation in patients (1 reported sporadic joint pain like our patient) without evidence of abnormalities characteristic of the highly aggressive hepatosplenic gamma/delta T-cell lymphoma

FOLLOW UP CONTINUED

- Joint pain resolved after one day, has not recurred
- Blood counts normalized after splenectomy
- Ongoing monitoring with hematology; follow up with me monitoring for RA sx



LEARNING POINTS

- Felty's syndrome = RA, splenomegaly, neutropenia
  - Often seen in longstanding seropositive disease with extra-articular manifestations
  - Treatment = MTX, rituximab, other DMARDs; splenectomy if refractory
- Expanded LGL seen in RA with similar presenting features to FS
  - Look for LGL leukemia by peripheral smear, flow cytometry, evidence of a clonal population of LGL, STAT3 mutation
- Be suspicious of atypical presentations of rare diseases