71-year-old male with rash

Duncan F. Moore, MD
Rheumatology Fellow, PGY-5
Massachusetts General Hospital
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MGH 1811
MASSACHUSETTS GENERAL HOSPITAL
RHEUMATOLOGY

Disclosures

- None

HPI – 71 yo M w/ rash

3-4 months PTA

- Progressive weight loss

2 months PTA

- Progressive fatigue, dry cough
- Dry, red eyes
- Xerostomia

1.5 months PTA

- Fever, night sweats x3 days
- Briefly hospitalized @ MGH
- CT chest --> tree-in-bud nodularities
- BAL --> H. influenzae
- Tx w/ cefpodoxime x2 wks

10 days PTA

- Hgb 7.0 (last 8.4)
- Cr 2.5 (baseline 0.6)

1 day PTA

- Outpt Pulmonology f/u
- Feeling well
- CT chest → nodularities resolving
- Hgb 5.9
- Cr 1.54

HPI – Presentation March 2021

- Sent in to hospital for eval of anemia, transfusion.
- Symptoms:
  - Denied symptoms at admit other than nasal congestion x 3-4 weeks.
  - Prior cough had completely resolved w/ cefpodoxime.
  - Gained weight since last admit.
  - No hemoptysis, fevers, chills, sweats, hematemesis, melena, or hematochezia.
- Hospital course:
  - Febrile x1 during first transfusion of pRBCs
  - Felt stronger after pRBCs x2.
  - Initial exam notable for 1+ edema b/l dorsa of feet. No rash.
  - EGD/colonoscopy hospital day 3: no overt pathology to explain blood loss
  - On hospital day 3, pt noted to have rash on b/l LEs.
    - *Given anemia, AKI, and rash, rheumatology was consulted for evaluation of possible vasculitis*

Additional Background

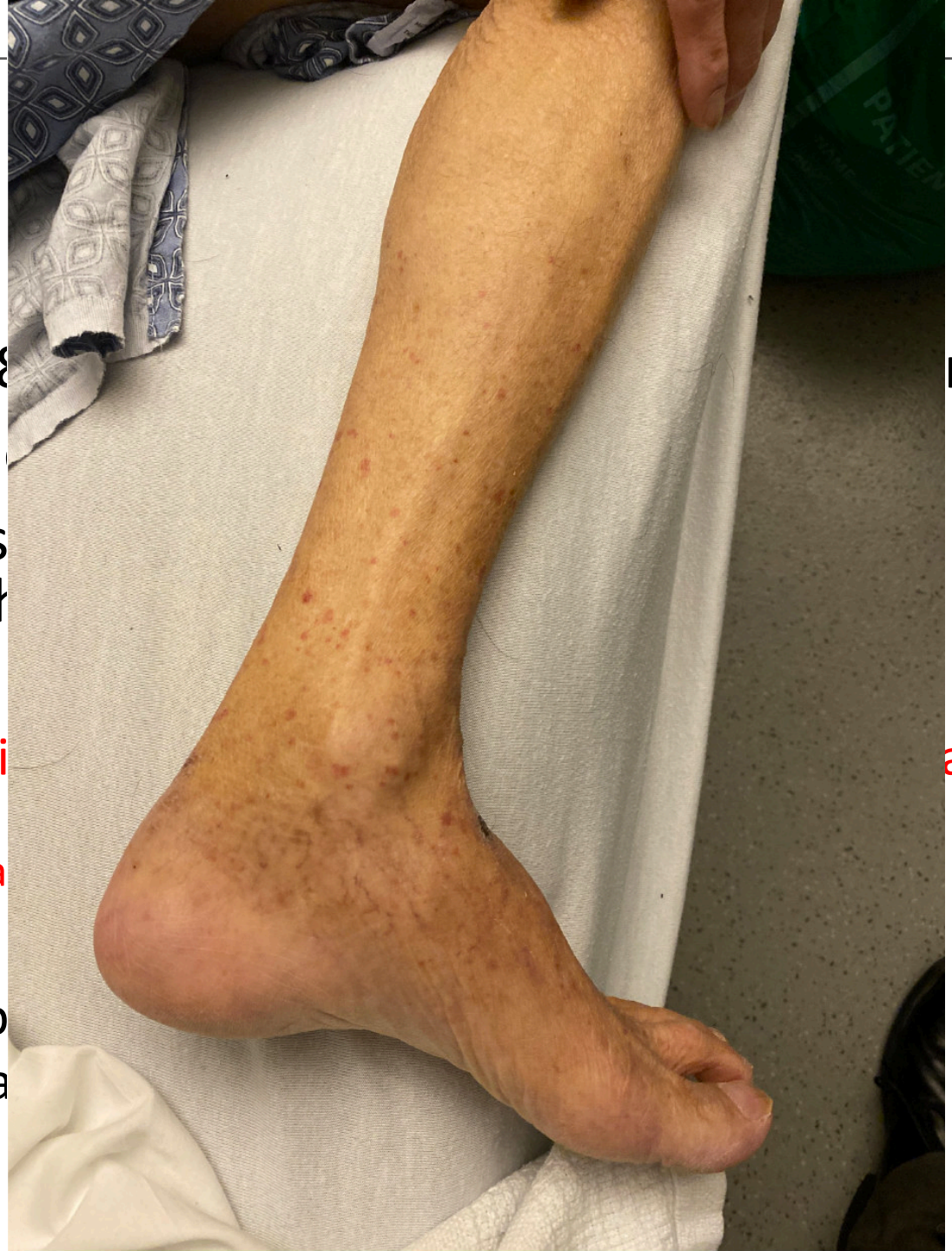
- PMH:
  - CVA, HTN, HLD, GERD
- Home Meds:
  - amlodipine 10mg daily, aspirin 325mg daily, simvastatin
  - Ocean nasal spray
  - Saliva substitutes q4hrs PRN
- FH: no family history of autoimmune disease
- SH: Born in Vietnam, speaks Cantonese. Retired restaurant worker. No recent travel.
  - Formerly drank alcohol in moderation, former smoker.

Additional HPI/ROS

- Additional HPI at index rheumatology consult hospital day 3:
  - Pt describes lower extremity rash onset 1.5 months PTA (during prior admission)
    - Lesions asymptomatic, transient on order of days-week, progressive in number/distribution
  - ROS positives:
    - dry mouth x2 months, marked relief with Biotene mouthwash
  - ROS negatives
    - nasal congestion, crusting, or epistaxis
    - oral ulcers
    - arthralgias
    - chest pain, dyspnea, palpitations
    - abdominal pain

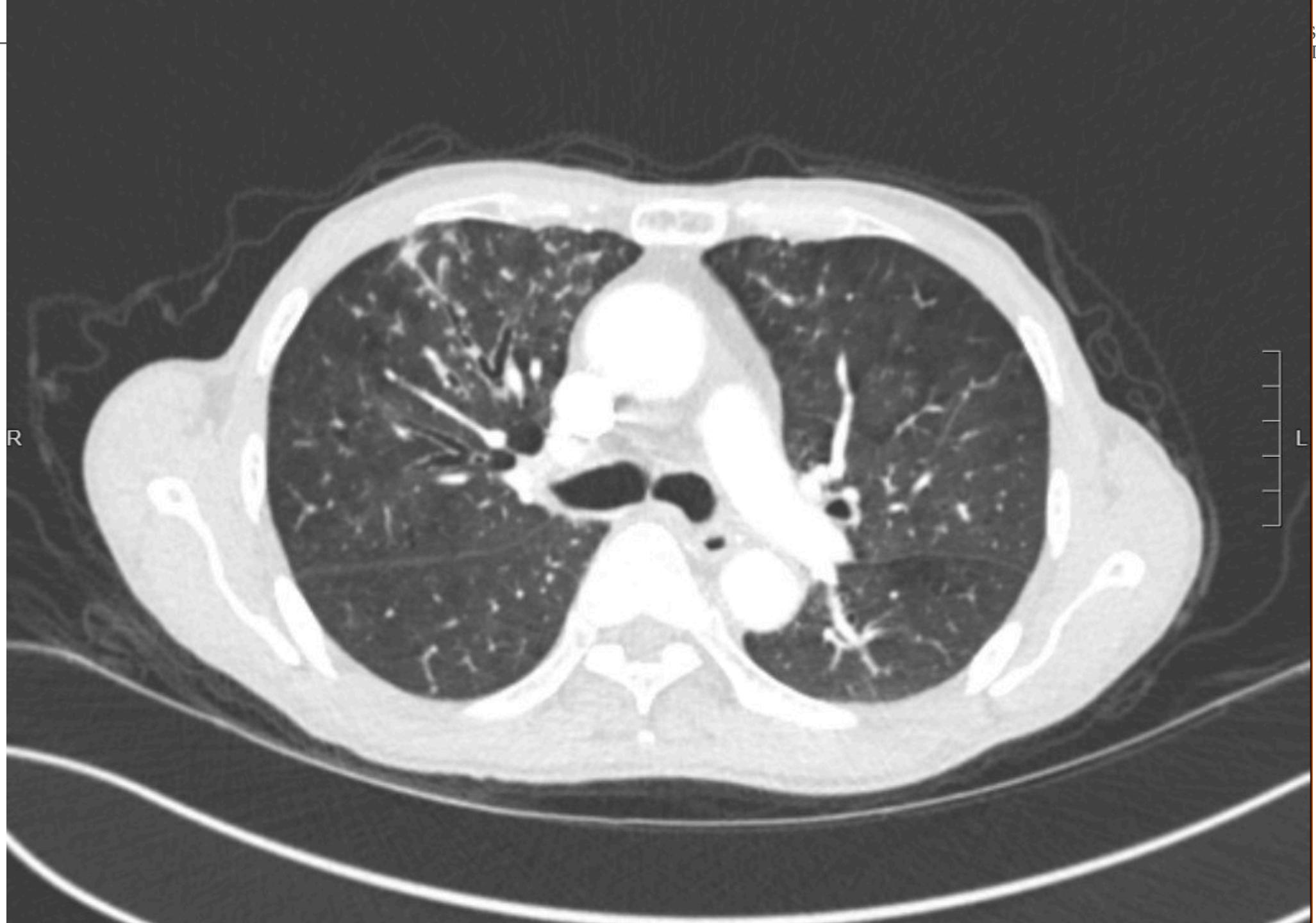
Exam

- VS: afebrile, HR 8 … room air
- Gen: comfortabl…
- HEENT: normal s… no oral ulcers; no lymphadenopath…
- Skin:
  - Distal b/l LEs wi… anching macular lesions
    - One lesion wa…
- MSK:
  - Bony hypertrop…
  - Tenderness of a…



Labs

- WBC 8.63, Hgb 8.8 (stable since pRBC x2), MCV 85, Plts 470
- CMP: notable for Cr 1.40
  - (1.57 at admit, 2.5 at 10 days PTA, 0.60 @ hospital discharge 6 weeks PTA)
- C3 79 (LLN 81), C4 < 9
- CRP 58, ESR 137 (no prior)
- Admit UA: RBCs 20-50, protein 1+, negative leukocyte esterase
- Coombs negative
- HBV core Ab positive; HBV S Ag/Ab, HCV negative; Quant Gold negative
- Additional PTA labs of note:
  - BAL 1/2021: bacterial culture + Haemophilus influenza; fungal and AFB cultures negative. RBCs noted on LUL lavage.
  - All blood, urine cultures, sputum cultures negative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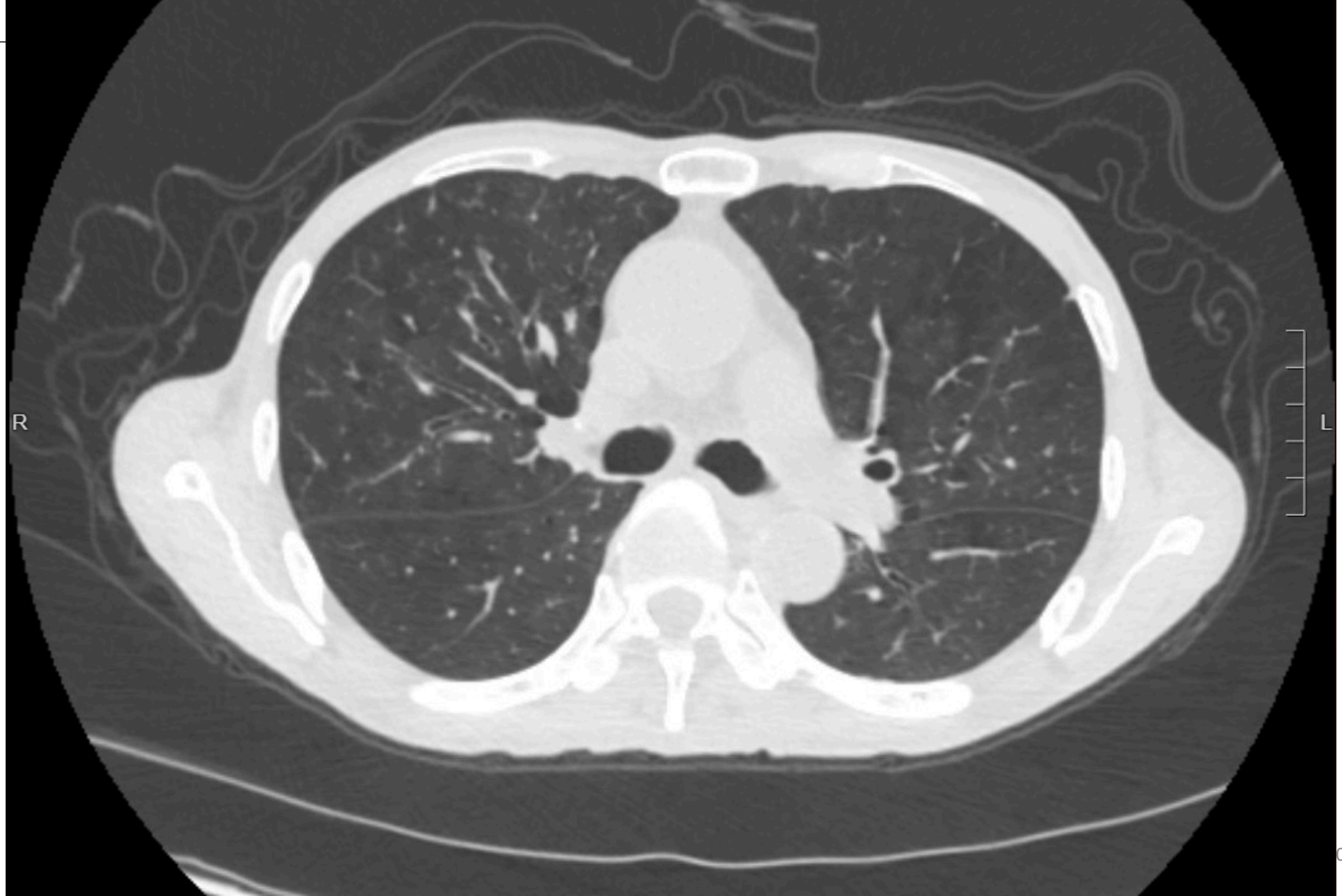
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Imaging

- CT chest (2/28/21):
  - Decreased tree-in-bud and consolidative opacities compared to January 2021, new compared to 2016. Findings likely represent resolving infection or aspiration. Subsegmental RIGHT middle lobe mucous plugging. No new or enlarging opacities.
- Bronchoscopy (1/19/21):
  - Some thick yellow secretions scattered throughout his RUL and RML in particular. A BAL was completed on 2 distal segments in the RML with adequate return. A second BAL was completed on the left apical segment with minimal return.
- CT abd/pelvis (1/13/21):
  - No primary tumor or metastatic disease in the abdomen/pelvis.
- CT chest (1/13/21):
  - New diffuse tree-in-bud nodularity throughout the lungs. These findings may represent multifocal infection (such as TB or non-tuberculosis mycobacterial infection) and/or recurrent aspiration.
    A new left apical nodule and adjacent consolidation may be from the same underlying process, however attention at follow up is warranted to exclude a neoplastic process.
  - Redemonstrated upper lobe predominant emphysematous changes and diffuse bronchial wall thickening.

Initial Summary

73 yo M with recent hospitalization for H. influenzae PNA s/p cefpodoxime treatment in setting of 3 months weight loss and 2 months sicca symptoms, found to have anemia, AKI, elevated ESR/CRP, hypocomplementemia, hematuria, and nonblanching macular rash on extremities.

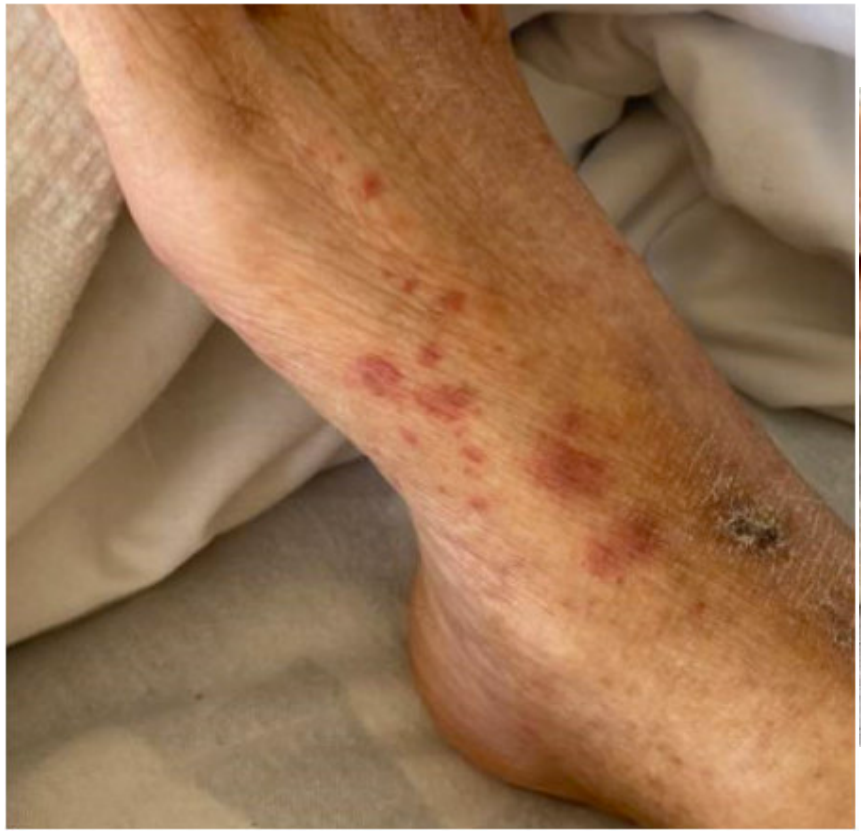
Initial Differential Diagnosis

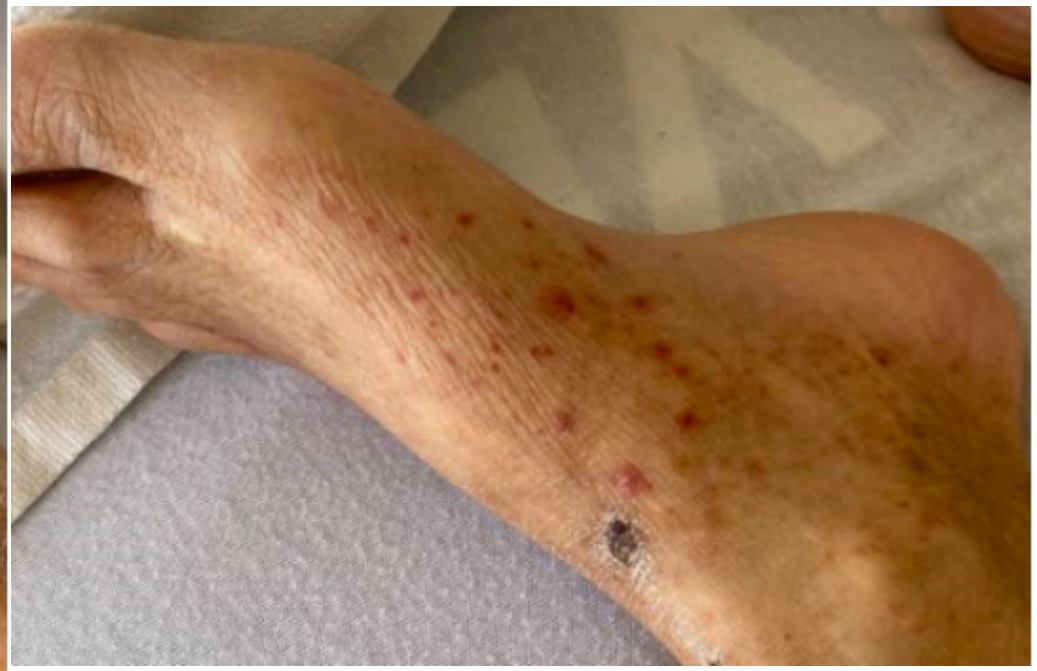
- Vasculitis
  - Hypocomplementemic:
    - Cryoglobulinemic vasculitis
    - Small vessel vasculitis secondary to Sjögren's Syndrome
    - SLE
    - Subacute bacterial endocarditis
    - Urticarial vasculitis
  - Non-hypocomplementemic:
    - IgA vasculitis
    - ANCA-associated vasculitis
    - Hypersensitivity vasculitis

Initial Workup

- Labs:
  - ANA
  - SSA, SSB
  - ANCA
  - SPEP
  - Urine total protein/Cr
  - Cryoglobulins
  - Hepatitis C viral load
  - RF
  - anti-GBM
  - Blood culture x2
  - Utox
- TTE
- Recommended Nephrology and Dermatology consultations

The next morning:





Skin biopsy results

- FINAL PATHOLOGIC DIAGNOSIS:
  A. SKIN BIOPSY, LEFT FOOT:
  Leukocytoclastic vasculitis (see note).

- DIRECT IMMUNOFLUORESCENCE OF SKIN (LEFT FOOT), PUNCH BIOPSY:
  Direct immunofluorescence examination shows vascular IgA and C3 deposition.
  Examination for IgG, IgG(whole), IgM and fibrinogen deposition is negative.

- *Note: These features together with direct immunofluorescence findings are supportive of IgA vasculitis. Clinical correlation is recommended.*

Workup results

- Labs:
  - ANA 1:2560 homogeneous
    - dsDNA, Smith, U1RNP negative
  - SSA/Ro 112, SSB/La 81
  - ANCA: positive, perinuclear staining, MPO+ 150 units, PR3+ 33 units (reference range < 20)
  - SPEP – normal pattern, elevated immunoglobulins, normal κ/λ ratio
  - Urine total protein/Cr 2.37
  - Cryoglobulins negative
  - Hepatitis B, C viral load negative
  - RF 79
  - *Repeat C3, C4 normalized before any tx*
  - lupus anticoagulant, anticardiolipin IgM/IgG, beta-2-glycoprotein 1 IgM/IgG negative
  - anti-GBM → negative
  - Blood culture x2 → negative
  - Utox negative
- TTE: small pericardial effusion

Question #1: What is the implication of dual MPO/PR3 positivity?

- Uncommon, with scant description in the literature.
  - Cases described in SBE, endocarditis, prolonged infections, etc.
  - Also described in cases of pachymeningitis, MCTD, tubulointerstitial nephritis
- Chou et al. (2015)[1]
  - Examined initial and final diagnoses of group of pts w/ dual PR3 and MPO positivity
  - In the end, found only 3 of 15 with AAV
    - among these 3, high MPO and low PR3
  - 8 with non-AAV autoimmune disease, 3 with recurrent infections, 3 with malignancy
- Think about drug-induced
  - dual MPO/PR3 positivity described in PTU use

1. J Clin Cell Immunol. 2015, 6:3

Interval summary

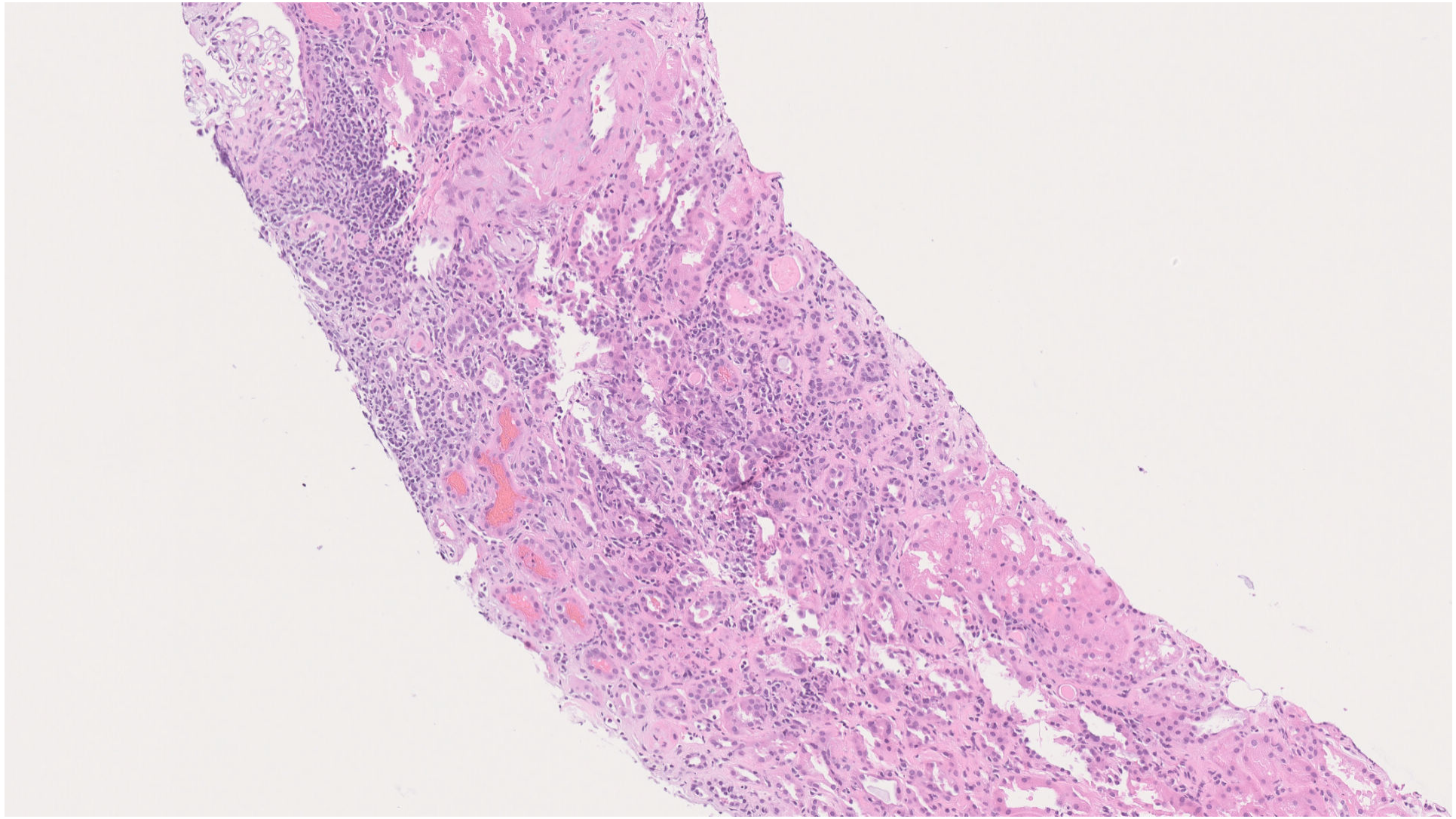
73 yo M with recent hospitalization for H. influenzae PNA s/p cefpodoxime tx in setting of 3 months weight loss and 2 months sicca sxs, found to have anemia, AKI, elevated ESR/CRP, hypocomplementemia, hematuria, proteinuria, +ANA/Ro/La/MPO/PR3 and cutaneous IgA vasculitis.

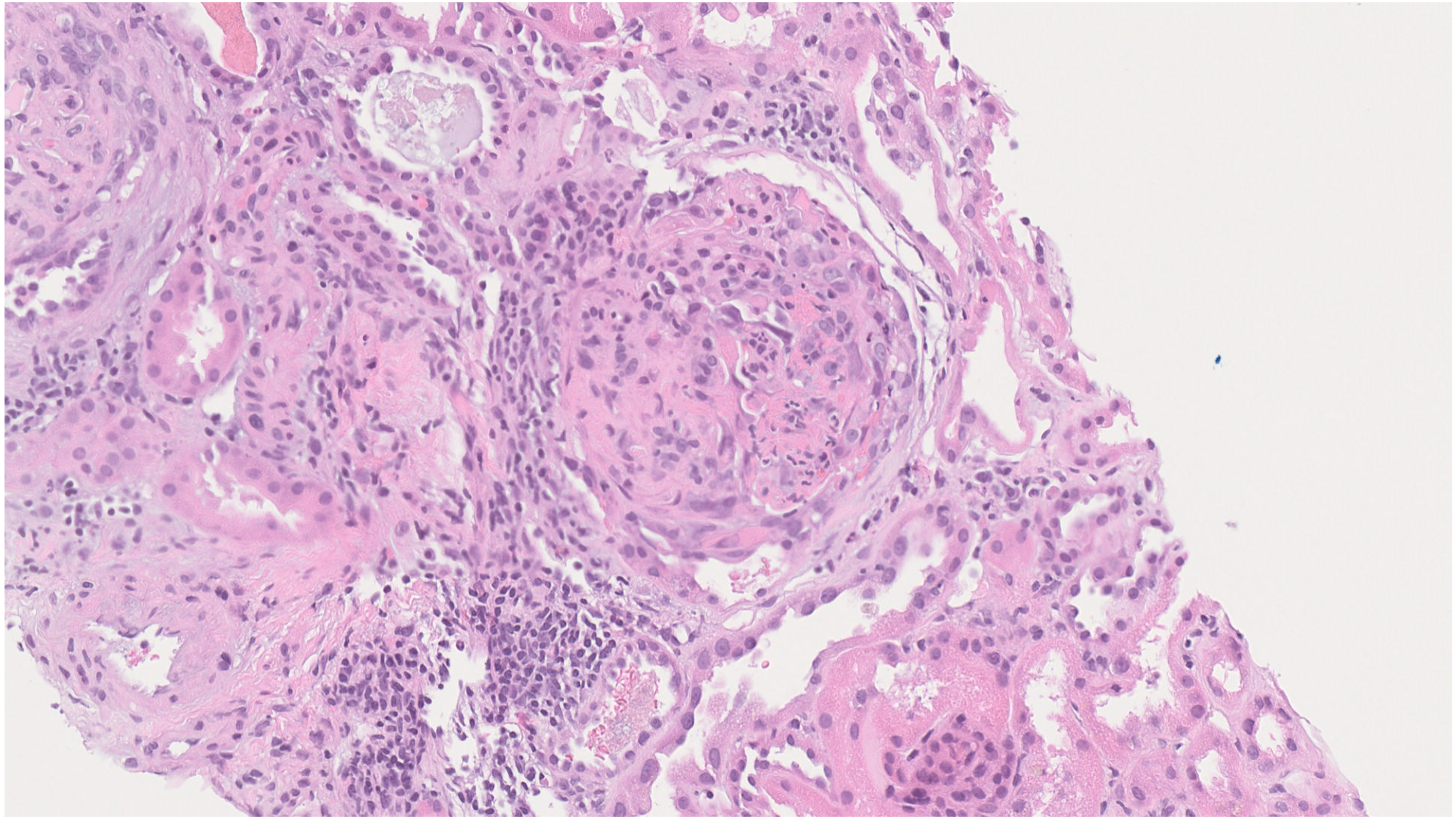
Inpatient course, continued

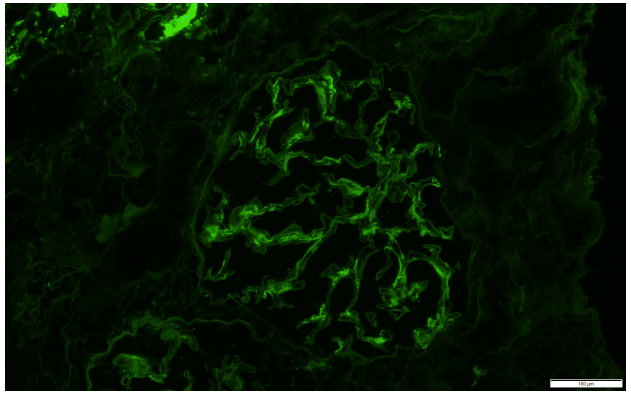
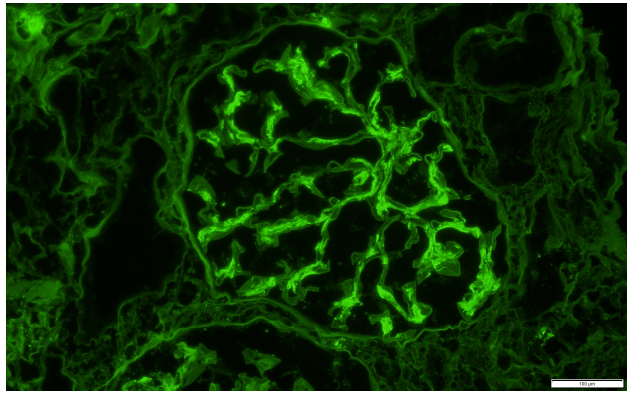
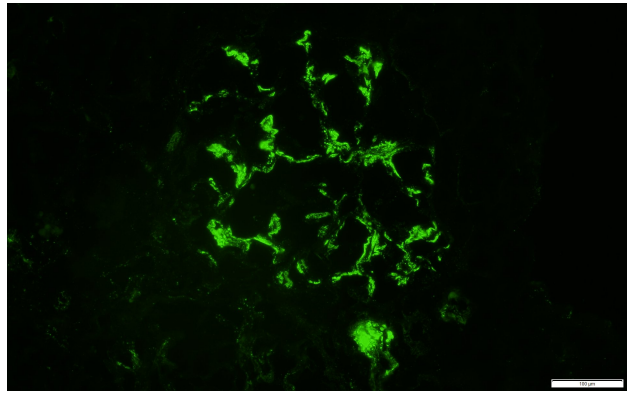
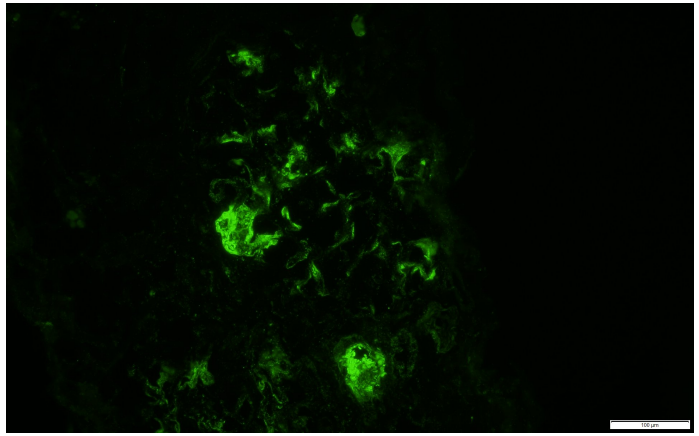
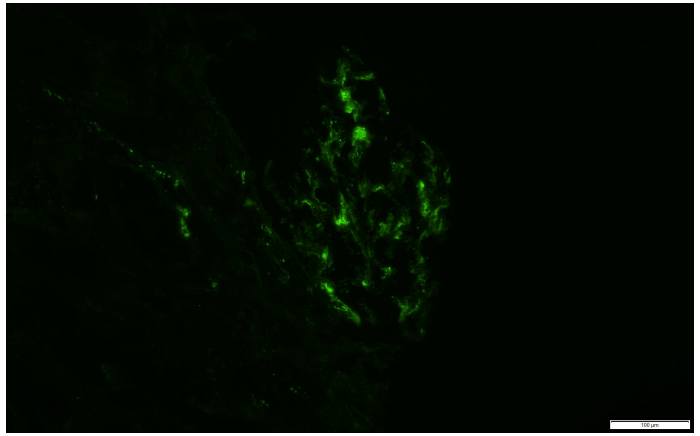
- Consensus with Nephrology: a vasculitis was driving palpable purpura, AKI, hematuria, but unclear which/how many vasculitides.
  - IgA vasculitis could be 2/2 recent PNA
    - Could explain purpura, AKI
  - Given ANA/SSA/SSB, consider concurrent nephritic syndrome 2/2 CTD
  - Given MPO/PR3, consider concurrent nephritic syndrome 2/2 AAV
- Empiric tx:
  - methylprednisolone 500mg IV x3 days
  - followed by prednisone 60mg PO daily
- While in-hospital, Cr peaked at 2.01, down to 1.80 at discharge.
- Planned for prompt outpatient renal bx (ASA washout).

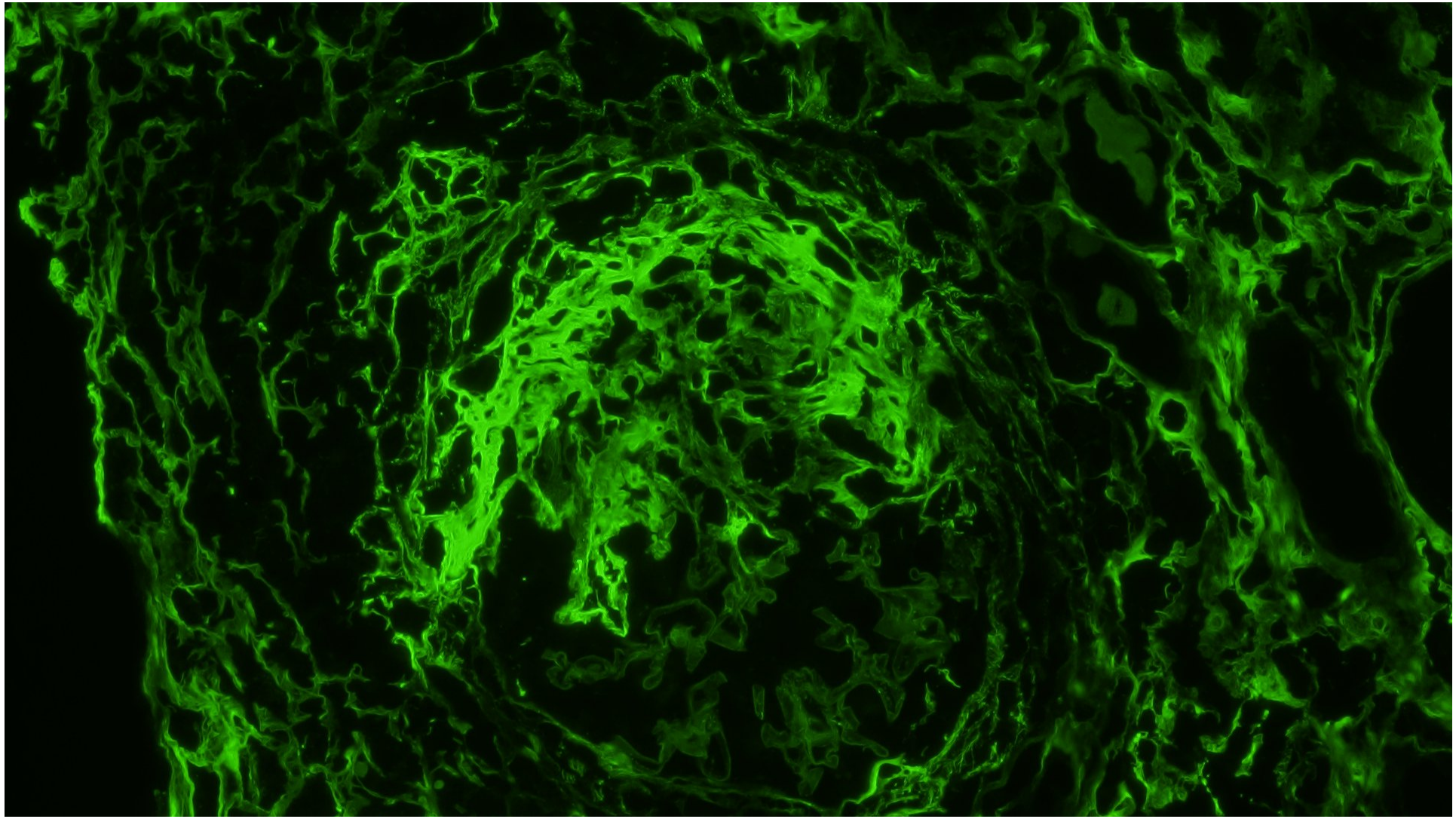
Renal biopsy – 10 days after index consult

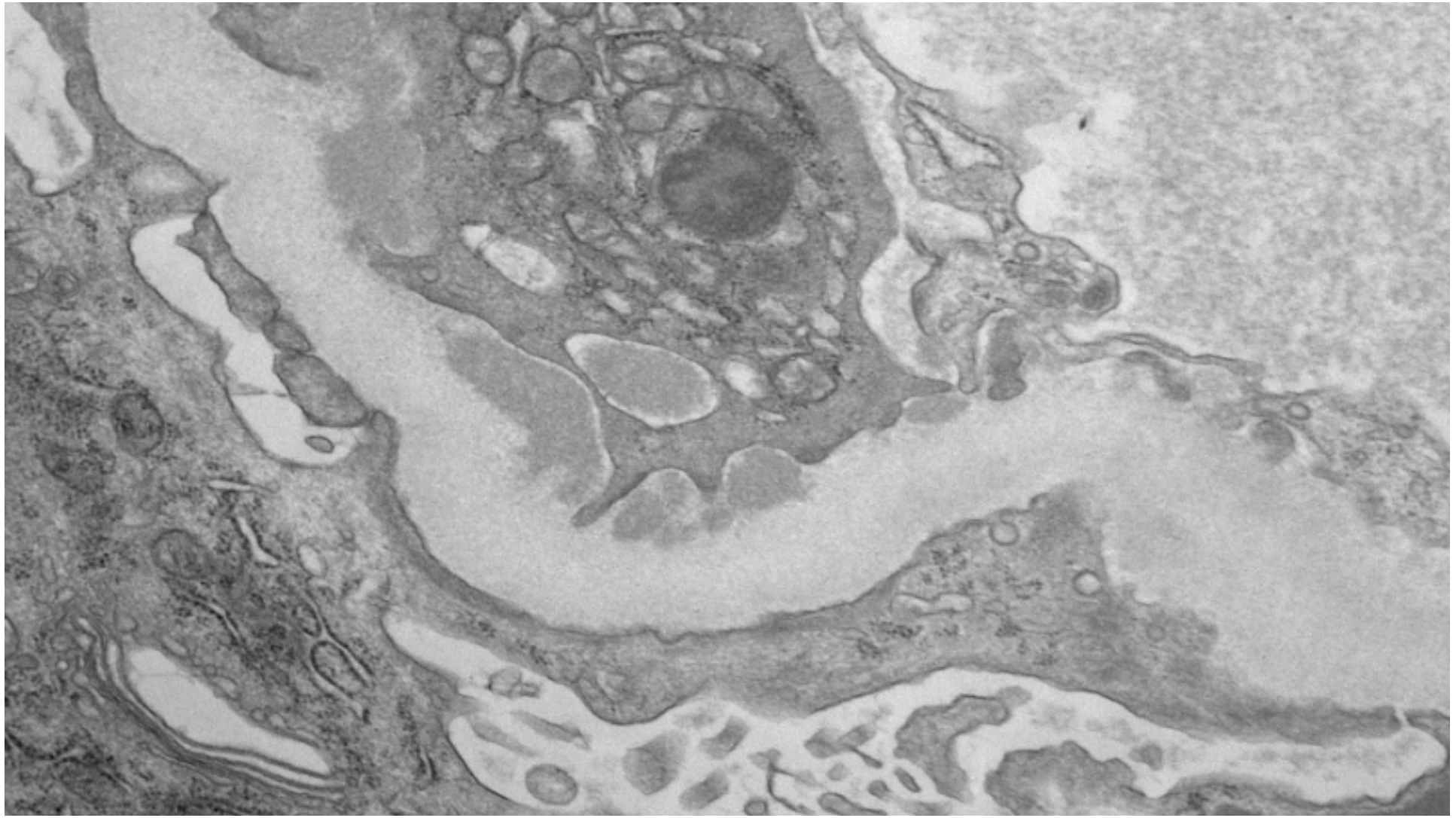
FINAL PATHOLOGIC DIAGNOSIS:
A. LEFT KIDNEY BIOPSY:
ACUTE CRESCENTIC NECROTIZING GLOMERULONEPHRITIS ASSOCIATED WITH:
-IgG, IgA, IgM, C3, C1q, KAPPA, AND LAMBDA GLOMERULAR DEPOSITS
-IgG, IgM, C3, C1q, KAPPA, AND LAMBDA TUBULAR BASEMENT MEMBRANE DEPOSITS
-ANCA POSITIVITY
CHRONIC PARENCHYMAL CHANGES, INCLUDING FOCAL SEGMENTAL GLOMERULOSCLEROSIS, 25.0%
GLOBAL GLOMERULOSCLEROSIS, AND APPROXIMATELY 10-20% INTERSTITIAL FIBROSIS AND
TUBULAR ATROPHY









Renal biopsy – 10 days after index consult

In summary, the biopsy shows a crescentic and necrotizing glomerulonephritis with a "full house" immune complex pattern by immunofluorescence. These findings by light microscopy and immunofluorescence are classically associated with lupus nephritis but are best interpreted in the context of the patient's individual rheumatologic presentation. If considered a manifestation of lupus nephritis, the findings would be considered representative of class IV lupus nephritis (diffuse lupus nephritis) with both acute and chronic lesions. Classification by the Modified NIH Lupus Nephritis Activity and Chronicity Scoring System is documented below. In the context of dual positive ANCA titers (i.e., antibodies against both myeloperoxidase and proteinase 3), a component of pauci-immune glomerulonephritis (i.e., a pauci-immune and immune complex "overlap" syndrome) cannot be ruled out and in fact may be suggested by the relatively low burden of subendothelial electron dense deposits by electron microscopy (1). Of note, dual positive ANCA titers have been observed in the setting of ANCA-associated vasculitis as well as other autoimmune diseases, drug reaction, infection, and malignancy (2).

Aggregated intracapillary platelets are noted in segmental capillary loops by electron microscopy. This finding may suggest a minor element of acute thrombotic microangiopathy, though clear fibrin thrombi are not appreciated. Ultrastructural evidence of podocyte injury is also present, as evidenced by widespread podocyte foot process effacement. The effacement is likely related to overlying crescents and underlying focal sclerosis due to the patient's above described glomerulonephritis, though other causes of podocytopathy may be considered based on the relationship of proteinuria to the patient's nephritic presentation.

1. Clin J Am Soc Nephrol. 2008 May;3(3):682-90.
2. J Clin Cell Immunol. 2015, 6:3

Question #2 – Can you have SLE-AAV overlap glomerulonephritis?

- Serologically:
  - among 566 SLE pts, MPO+ 9.3% and PR3+ 1.7% by ELISA (Galeazzi 1998)
- Pathologically, first described in a series by Nasr et al. (2008)
  - Review of 10 lupus nephritis cases from Columbia with: 1) prominent fibrinoid necrosis and crescents, 2) minimal to absent subendothelial deposits, 3) positive ANCA serologies
  - Laboratory features:
    - 8 pts fulfilled 4+ ARA criteria for SLE, 2 pts fulfilled 3 criteria
    - All pts ANA+
    - 9 pts w/ hypocomplementemia
    - 9 pts w/ ANCA result reviewable, all p-ANCA, by ELISA 5/5 with MPO+
  - Clinical features:
    - 2 pts w/ pulmonary hemorrhage; no extra-renal e/o vasculitis in other 8 pts
    - 2 pts on hydralazine
  - Path: subendothelial deposits rare or absent
  - Tx: all pts treated with CYC
  - ANCA titers became negative with tx in 5/6 pts tested

1. Clin Exp Rheumatol. Sep-Oct 1998;16(5):541-6.
2. Clin J Am Soc Nephrol. 2008 May;3(3):682-90.

Question #3 – Is IgA vasculitis associated with SLE or AAV?

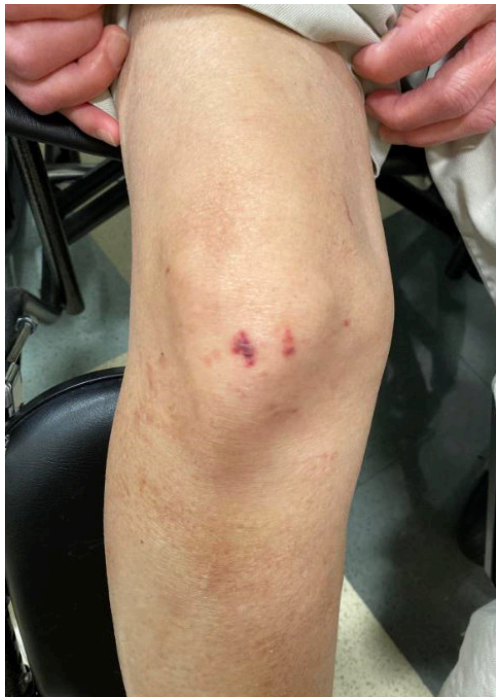
- *The predominance of IgA deposition uniquely characterizes IgA vasculitis*.
- IgA vasculitis is not reliably associated with SLE
  - Murata *et al.* describes 15 pediatric cases of juvenile SLE preceded by IgA vasculitis[1]
  - Case report of IgA vasculitis w/ renal involvement in adult w/ known SLE[2]
- ANCA positivity is rarely seen in IgA vasculitis
  - One 2019 retrospective: 5 of 86 (5.8%) IgA vasculitis pts w/ +ANCA (all +MPO)[3]
    - but no difference renal involvement or renal histology
    - none classified as having AAV

1. BMC Pediatr. 2019 Nov 26;19(1):461.
2. BMJ Case Rep. 2015 Sep 9;2015
3. Rheumatol Int. 2019 Nov;39(11):1927-1936.

Clinical follow-up – 8 days post-biopsy

- Continues to develop new LE rash lesions; otherwise asymptomatic
- Labs
  - WBC 22 (93% neutrophils), Hgb 9.8, Plts 414
  - CMP: notable for Cr 1.39 (from 1.8)
  - ESR 55, CRP 1.3
  - UA (POC): 3+ blood, 2+ protein
  - Total protein/Cr 2.41
  - ANCA

	MPO (rr < 2.8)	PR3 (rr < 20)
3/7/21	150	33
3/26/21	86	131



Subsequent outpatient management

- Pathology conference conducted with Renal and Rheum
- Impression:
  - Pathology most c/w lupus nephritis.
    - ANA, hypocomplementemia supportive
  - Cutaneous IgA vasculitis
  - Difficult to say whether or not there is concurrent AAV
    - Relatively few subendothelial deposits
    - Strongly-positive serologies, including increasing PR3+
      - But persistent dual-positive
- Treatment options:
  - Tx both SLE and AAV with steroids + CYC
  - Tx both SLE and AAV with steroids + RTX
  - Tx SLE w/ steroids + MMF, monitor response
    - add CYC or RTX after COVID-19 series completed if concern for non-response or with rising ANCA titers

Subsequent clinical follow-up

- Treatment: MMF 1500mg BID, prednisone (tapered to off by 7/31)
- Cr stabilized at ~1.5 (eGFR 40s), proteinuria persistent (UPCR ~3.00 mg/mg)
- ANCA

	MPO (rr < 2.8)	PR3 (rr < 20)
3/7/21	150	33
3/26/21	86	131
4/28/21	21	231
5/24/21	5.3	180

Final diagnosis

- Cutaneous IgA vasculitis with concurrent class IV lupus nephritis and possible overlap glomerulonephritis secondary to AAV with +MPO and +PR3 (PR3-predominant)

Key points

- IgA vasculitis is not reliably associated with +ANCA serologies or SLE.
- The DDx for dual-MPO/PR3 ANCA positivity includes non-AAV autoimmune disease, infection, malignancy, and drug effect.
- It is hypothesized that SLE and AAV can overlap as glomerulonephritis in the kidney.

Tissue pathology often can clarify the underlying vasculitic process, but it is not absolute in its diagnostic certainty.

Multiple primary vasculitides can co-occur. Heed Hickam's dictum!

Thank you!

dmoore24@mgh.harvard.edu