A 29-YEAR-OLD MAN PRESENTING WITH PALPABLE PURPURA, GENERALIZED SWELLING, AND KIDNEY INJURY

Cyrus Faridi, DO

OHSU Rheumatology Fellow

CASE

29 year old male, no past medical history

Presents to OSH ED w/ 4-5 days of LE purpuric rash which migrated to trunk + upper extremities, arthralgia, hypertension, UE + LE extremity swelling

3 weeks of viral URI symptoms which had improved by the time of visit

CMP WNL, CBC WNL, UA w/ protein (urine protein 254 mg/dL,), blood, granular casts, leukocyturia, RF 66.8, ANCA/MPO/PR3 negative, atypical p-ANCA 1:80, complement WNL

Given clinical stability and lack of clear systemic involvement, discharged home with dermatology and nephrology OP follow up

INITIAL DIFFERENTIAL

- IgA vasculitis (tetrad of palpable purpura, arthalgia/arthritis, abdominal pain, and renal involvement)
- ANCA-associated small vessel vasculitis (AAV) - microscopic polyangiitis, granulomatosis with polyangiitis
- Immune-complex mediated leukocytoclastic vasculitis – drug-induced, infection-related, autoimmune disease, malignancy
- Cryoglobulinemic vasculitis – palpable purpura, arthralgia, renal involvement
- Catastrophic antiphospholipid syndrome – palpable purpura, multiorgan thrombosis, AKI
- Thrombotic microangiopathies - TTP (p/w plts <30, cr <2) /HUS (p/w plts > 30, cr >2), DIC
- CTD-associated secondary vasculitis – SLE, Sjogren's, RA
- Sepsis with DIC – prolonged PT/PTT, low fibrinogen, elevated D-dimer, thrombocytopenia
- Primary infectious – tick borne illness, syphilis, hepatitis, chlamydia
- Paraneoplastic vasculitis

CMP WNL, CBC WNL, UA w/ protein (urine protein 254 mg/dL,), blood, granular casts, leukocyturia, RF 66.8, ANCA/MPO/PR3 negative, atypical p-ANCA 1:80, complement WNL

Given clinical stability and lack of clear systemic involvement, patient was discharged home with dermatology and nephrology OP follow up

How does this change your differential?

CASE CONT.

Patient again opresents to OSH ED 5 days later with progressively worsening rash, generalized edema including scrotal involvement

CBC now with anemia, CMP with cr 2.03 (baseline 1), eGFR 45,

UA micro with blood, protein, white cell casts, blood cx negative

per RN report has dark tea colored foamy urine

CRP 111.66, ESR 42, PT/INR nl

CK 319, TSH 1.8

Patient is subsequently transferred to OHSU to further evaluation.

PICTURE

Patient was transferred in stable condition.

ESR 34, CRP 75

ANA, ANCA negative

C3, C4 WNL

HIV negative

Hep B, Hep C, HIV serology negative

Anti-streptolycin O 120

COVID negative

Cryoglobulin positive, Type III cryoglobulin with polyclonal IgG and IgA

UPC -> 1.17, Urine protein 142 mg/dL

UA micro with blood and protein

Infectious work-up (Cryptococcal, fungal antibodies, blood cx, RPR, TB) all negative

SPEP - no monoclonal spike, elevated kappa and lambda night chains with normal ratio

Fibrinogen nl, haptoglobin elevated, LDH mildly elevated

SSA, SSB, CCP, parvovirus negative, EBV negative

Imaging:

CXR: Left mid-lung ground-glass opacity with a possible cavitary lesion

- Interesting: Patient had mentioned something about hemoptysis...

CT chest: Multifocal bilateral peribronchovascular nodular consolidative opacities, many with central cavitation, including dominant cavitary lesion in the peripheral left upper lobe.

US kidney: no hydronephrosis or RAS

CONSULTANTS (BESIDES RHEUM)

Derm thought presentation was most consistent with IgA vasculitis vs leukocytoclastic vasculitis and recommended skin biopsy

Derm path – **leukocytoclastic vasculitis** (focal perivascular deposits of fibrin in the upper and mid-dermis associated with perivascular inflammation with neutrophils and eosinophils.)

Direct immunofluorescence: faint granular deposition of **IgA, IgM, and C3** (IgA deposition is not stronger in intensity as compared to those immunoreactants)

Nephrology – Highest suspicion for IgA, did not think kidney bx was necessary given resolved AKI and subnephrotic range proteinuria, given lisinopril

Infectious disease – consulted to rule out infectious causes

SKIN BIOPSY

- IgA vasculitis (post-viral trigger, purpura, arthalgia, renal involvement)
- ANCA-associated small vessel vasculitis (AAV) - ANCA/MPO/PR3-, no chronic sinusitis or difficult to treat asthma, ?pulmonary involvement, renal involvement
- Immune-complex mediated leukocytoclastic vasculitis – drug-induced, infection-related, autoimmune disease, malignancy
- Cryoglobulinemic vasculitis – palpable purpura, arthralgia, renal involvement, high RF and purport, nl complements
- CTD-associated secondary vasculitis – SLE, Sjogren's, RA; negative ANA, no hx of untreated RA
- Thrombotic microangiopathies – normal platelets, PT/INR, high fibrinogen, moderately elevated LDH
- Sepsis with DIC – prolonged PT/PTT, low fibrinogen, elevated D-dimer, thrombocytopenia
- Primary infectious – tick borne illness, syphilis, hepatitis, chlamydia etc negative; no known exposures
- Paraneoplastic vasculitis – no risk factors for mamignancy
- Catastrophic antiphospholipid syndrome – no multiorgan thrombosis,

Patient rash, edema, and kidney function were stable until…

He developed rapidly expending effusion of the forehead and upper eyelids along fascial planes

CT head negative other than large bifrontal scalp effusion

MRV negative for dural venous thrombosis

ENT evaluated and did not think angioedema; ophthalmology not concerned for primary ocular condition

Repeat

- UA with worsening hematuria, proteinuria
  - UP 790 mg/dL, UPC 3.99
  - Cr remained stable

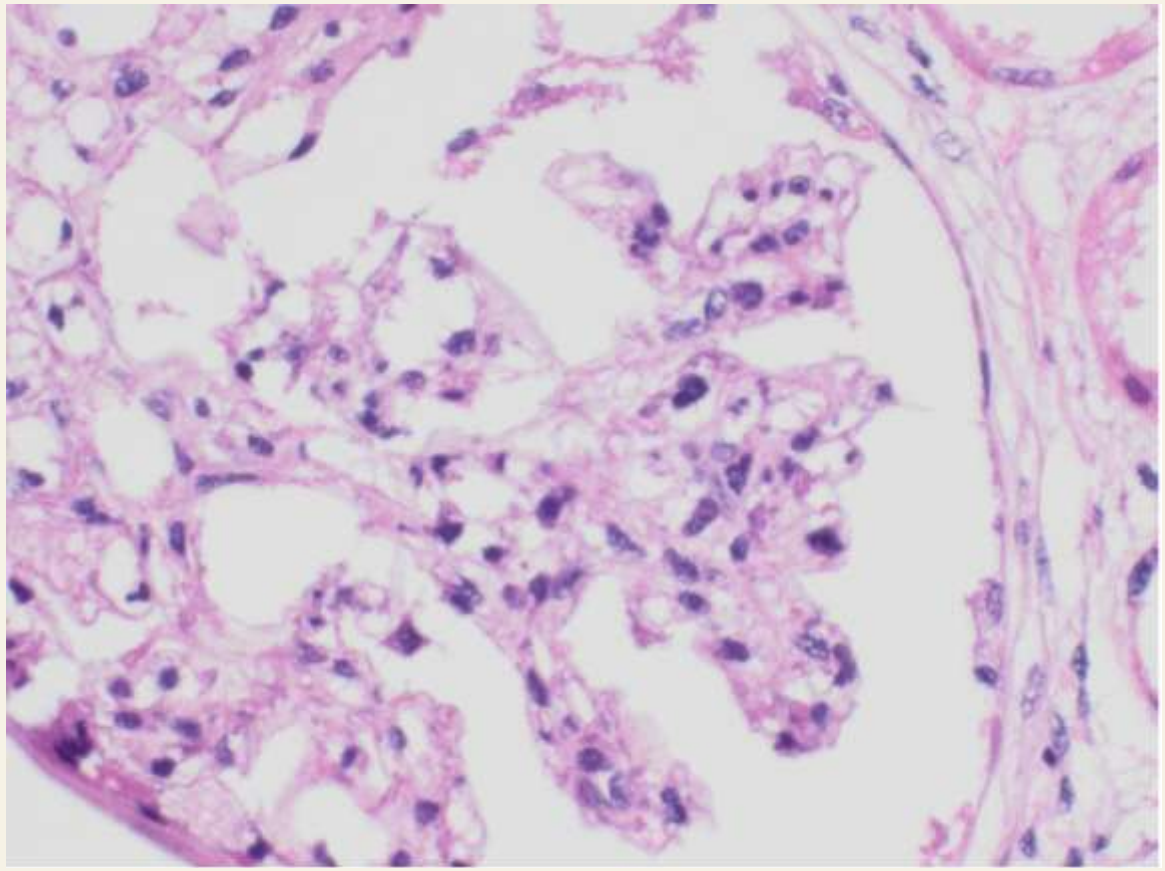
Kidney biopsy:

IgA and C3 dominant glomerulonephritis, moderate IgG and IgM

Evaluation was hampered by the lack of renal cortex in the sample submitted for light microscopy

The pathologic findings could fit well for IgA and C3 dominant bacterial infection related glomerulonephritis, a process that in some patients can behave like a systemic immune complex mediated vasculitis with associated cutaneous leukocytoclastic vasculitis and occasionally a detectable cryoglobulin. Conversely, the possibility of an unusual (given clinical picture, infection, cryoglobulin, degree of IgM and C3 staining) IgA nephropathy/IgA vasculitis cannot be entirely excluded but is not favored at this time.

KIDNEY BIOPSY



Ultimately diagnosed with staphylococcus-associated glomerulonephritis with cryoglobulinemic features?

Treated with 4 weeks of linezolid with imrpvement in lung, kidney, and cutaneous manifestations

INFECTION-RELATED GLOMERULONEPHRITIS

Terminology

Includes: post-streptococcal GN, staphylococcus-associated GN, GN associated with endocarditis or with viral (Hep B, C, HIV), fungal, protozoal, or parasitic infections

Poststreptococcal GN - kidney disease typically begins after the infection has either resolved spontaneously or been effectively treated

In this case, we have **staphylococcus-associated GN** - occurring while patient is still infected

Additional entity is IgA-dominant infection-related glomerulonephritis - can occur with staphylococcal infection; distinct morphologic variant of infection-related glomerulonephritis characterized by dominant or codominant glomerular deposits of IgA

PATHOGENESIS

- Remains largely unknown
  - Likely involves glomerular deposition of preformed circulating immune complexes
- Prolonged antigenemia, there is a greater opportunity for immune complexes to form in the circulation, which then deposit causing **glomerulonephritis** and, in some cases, **cutaneous vasculitis**
- Immune complex mediated disease, antigen component of the immune complex is derived from the infective agent
- Staphylococcus-associated glomerulonephritis requires continued antigen production and therefore continued active (and usually prolonged) infection to perpetuate the kidney inflammation. (1, uptodate)
- If the infection is effectively treated, the activity of the glomerulonephritis should eventually abate
- A small genomic study found a higher prevalence of *agr* mutations (known to promote prolonged bacteremia and secondary seeding of infection), reduced beta-hemolytic activity, and higher biofilm formation in blood culture isolates from patients with staphylococcus-associated glomerulonephritis compared with those from patients with staphylococcal infection without glomerulonephritis (2)

EPIDEMIOLOGY

Rare (occurring in less than 1% of kidney bx), occurring more commonly in middle-aged or older adult patients

Persons with prdisposition to staphylococcal infection such as diabetes, alcoholism, cancer, or intravenous drug addiction

CLINICAL MANIFESTATIONS

Initial presentation: Peripheral edema in ~ 50 percent of patients, new-onset hypertension in 12 to 29 percent

Urine sediment with hematuria in almost all patients +/- leukocyturia and red cell casts

- 22 to 35 percent have overt nephrotic syndrome

Cutaneous vasculitis can occur in patients with staphylococcus-associated glomerulonephritis, **imitating IgA vasculitis (Henoch-Schönlein purpura) or antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis**

Most common sites of infection:

Heart/endocarditis – 18 patients (23 percent)

Skin, including leg ulcers and cellulitis – 17 patients (22 percent)

Bone/osteomyelitis – 17 patients (22 percent)

Lung/pneumonia – 6 patients (8 percent)

Visceral abscess – 6 patients (8 percent), Urinary tract infection – 2 patients (6 percent)

DAIGNOSTIC EVALUATION

Lab findings:

- Hematuria, leukocyturia, mean protein excretion 3 g/day
- Hypocomplementemia
  - low C3 and C4 are not characteristic of IgA nephropathy, ANCA-associated vasculitis, or anti-GBM disease
  - hypocomplementemia combined with an active urine sediment can be seen with other diseases (LN), C3 GN, mixed cryoglobulinemia
- Positive serologic testing for ANCA can be observed in 25 to 30 percent of patients (typically iso infectious endocarditis and antibodies against PR3)

Serologic testing:

Serum C3 and C4 complement levels, ANA, anti-dsDNA antibody, ANCA, Anti-glomerular basement membrane (anti-GBM) antibodies, Serology for hepatitis C virus, hepatitis B virus, and HIV, Serum cryoglobulins, Serum free light chains and serum protein electrophoresis with immunofixation

- Pretty typical of vasculitis work-ups

DIFFERENTIAL

- C3 GN (distinction: hematuria can occur a few days after URI; prevalence of MPGN, persistence of low C3)
- IgA-dominant staphylococcus-associated GN vs primary IgA nephropathy (no prominent IgA deposits)
- Post-strep GN (more typical in kids, cutaneous vasculitis is not a manifestation of this)

BX PITFALLS TO CONSIDER

Biopsy features can resemble primary IgA nephropathy and Henoch-Schönlein purpura nephritis

This is clinically relevant because of the crucial difference in the therapeutic approach.

- Clinical context is important: axtive staph infection, older age, diabetes, hypocomplementemia suggests infection related disease

The diagnosis of SAGN is further complicated by the variability in the degree of glomerular IgA (and C3) staining, the extent of electron dense immune-type deposits, and positive ANCA serology in some patients (3)

Satoskar AA, Suleiman S, Ayoub I, Hemminger J, Parikh S, Brodsky SV, Bott C, Calomeni E, Nadasdy GM, Rovin B, Hebert L, Nadasdy T. Staphylococcus Infection-Associated GN - Spectrum of IgA Staining and Prevalence of ANCA in a Single-Center Cohort. Clin J Am Soc Nephrol. 2017 Jan 6;12(1):39-49. doi: 10.2215/CJN.05070516. Epub 2016 Nov 7. PMID: 27821389; PMCID: PMC5220658.

HISTOLOGY

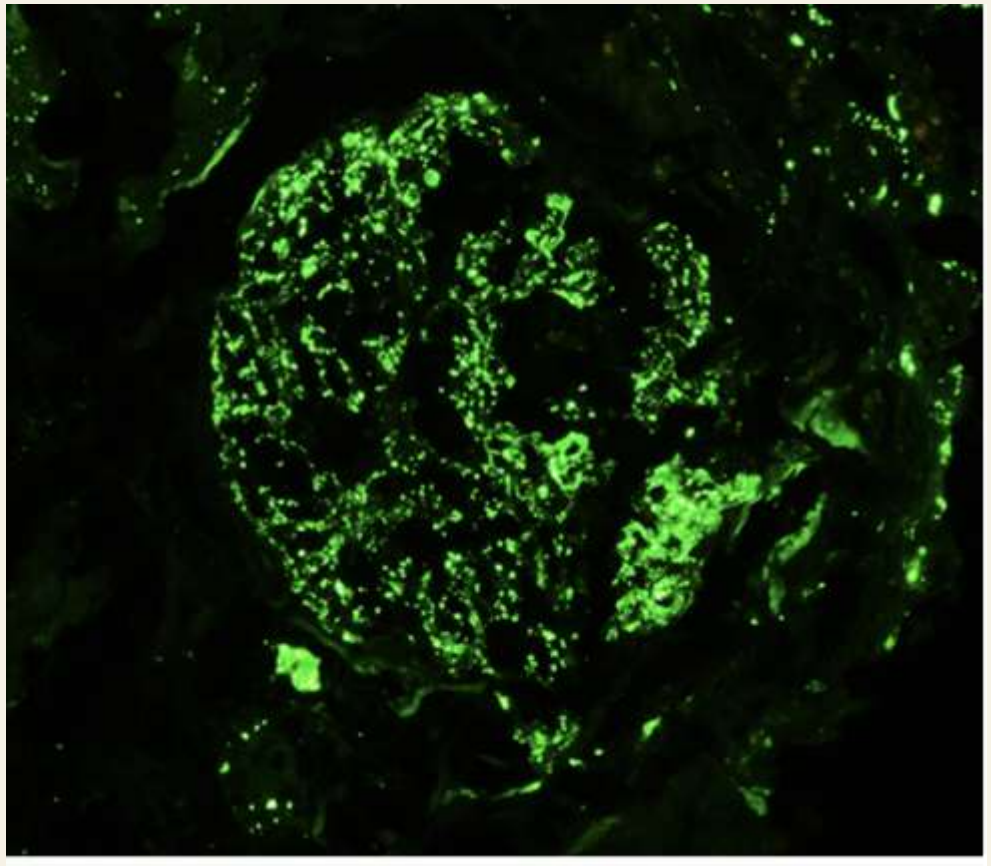
Light microscopy - diffuse endocapillary proliferative and exudative glomerulonephritis with more than 50 percent of glomeruli showing occlusion of the peripheral capillaries by endocapillary

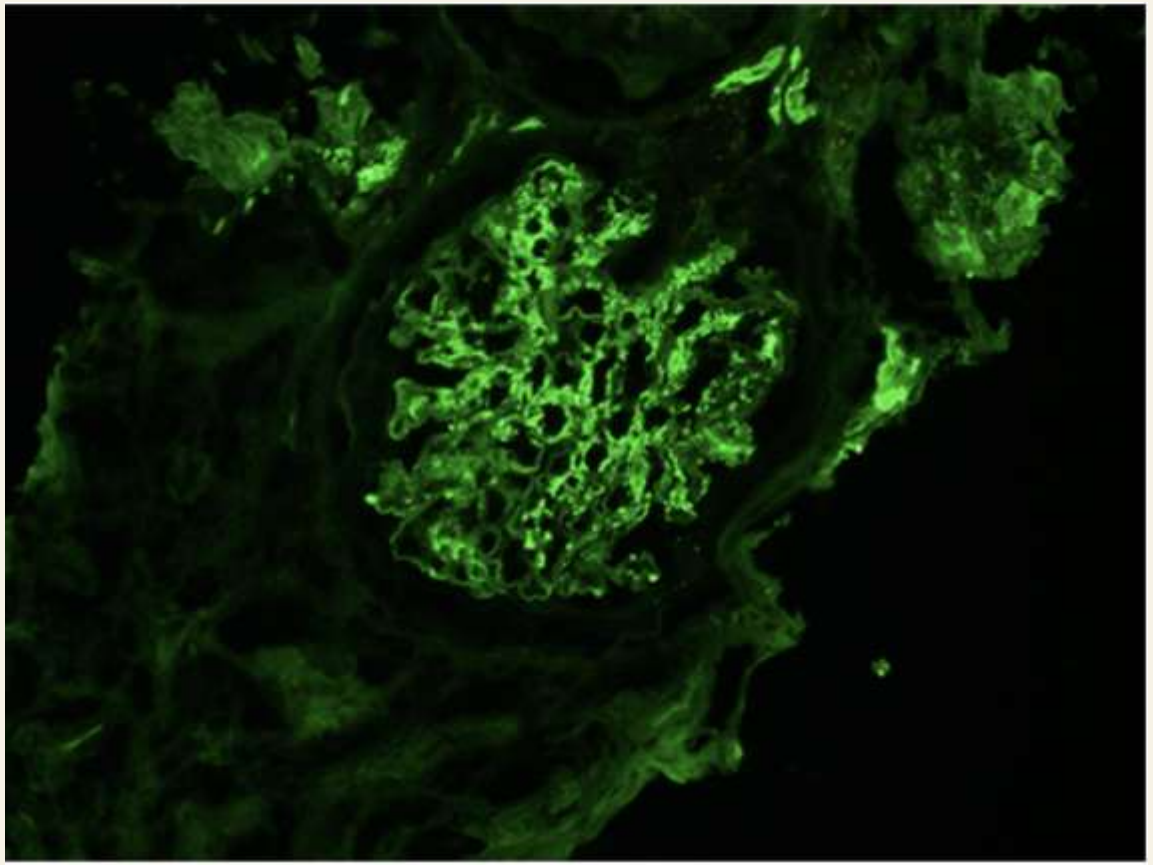
hypercellularity, including abundant intracapillary infiltrating neutrophils

Immunofluorescence microscopy - C3 dominant or codominant (with IgA or IgG) glomerular staining; can also have IgA dominate disease (confusing picture)

- staphylococcus-associated glomerulonephritis may be difficult to distinguish from C3 glomerulonephritis (if no significant immunoglobulin deposition)

Electron microscopy - large, hump-shaped subepithelial electron dense deposits





TREATMENT

Focus on eradicating the infection, relieving symptoms, and controlling hypertension and edema. **We do not use immunosuppressive therapy in such patients.**

Retrosepctive study: 109 older adults (46 with SAGN), 22 treated with GC, no association between GC and kidney outcomes

Postinfectious glomerulonephritis in the elderly.

Nasr SH, Fidler ME, Valeri AM, Cornell LD, Sethi S, Zoller A, Stokes MB, Markowitz GS, D'Agati VD

J Am Soc Nephrol. 2011;22(1):187.