Title

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Journal

Proceedings of UCLA Health, 22(1)

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Publication Date

2018-08-29

CLINICAL VIGNETTE

IgA Dominant Post Infectious Glomerulonephritis Resulting in an Aggressive Course and End Stage Renal Disease Despite Treatment

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Introduction

Post infectious glomerulonephritis (PIGN) is an immune response to an infection that results in inadvertent glomerular injury.[1] This phenomenon occurs commonly with bacterial infections, classically with nephritogenic strains of group B streptococcus.[2] However, viral infections can trigger post infectious glomerular disease as well. Though pathologically distinct, a prominent example of post viral renal injury would be HIV immune complex disease (HIVIC).[3]

Classic PIGN occurs two weeks after initial infection, since it takes time to generate antibodies against the offending pathogen. The timing of onset helps differentiate PIGN from IgA nephropathy (due to glycosylation defects), since both can present with hematuria in context of recent infection driving an underlying auto immune response. There is some overlap between both IgA nephropathy exacerbation and post infectious glomerulonephritis.[4] We present a complex case that pathologically and clinically included both IgA nephropathy and PIGN on the differential. The patient had a rapidly progressive and aggressive glomerulonephritis that had clinical and pathological features of crescentic IgA nephropathy (Henloch Schonlein Purpura- [HSP]) and PIGN.

Case Report

A 57-year-old man with hypertrophic cardiomyopathy, hypertension, and COPD with recent exacerbation presented to the ER with acute onset dyspnea, nonproductive cough, and wheezing that improved with IV methylprednisolone, nebulizer treatments, and intravenous fluids. The patient also noted bilateral lower extremity swelling and tea-colored brown urine over the past few days. He did not have dysuria, frequency, nor cloudy or malodorous urine.

Past medical history also included hyperlipidemia and right ear schwannoma diagnosed three months ago. Medications at home were gentamicin ear drops, fluticasone-salmeterol, atorvastatin 40mg, aspirin 81mg, monetelukast 10mg, and omeprazole 20 mg, and prn albuterol inhaler. Upon admission, vital signs showed a temperature of 98.7 °F, heart rate 80 beats/minute, respiratory rate 16 breaths/minute, blood pressure 149/90 mm Hg, O2 saturation 97% on room air.

Physical examination revealed no conjunctival pallor, no elevation of the jugular venous pressure, no accessory muscle use, clear lungs, normal heart sounds, no costovertebral angle tenderness, unremarkable abdominal exam, and 1+ lower extremity ankle edema. There was no petechiae, rash, or erythema.

Significant laboratory findings included a BUN 35 mg/dL, serum creatinine 1.49 mg/dL (baseline 0.8 mg/dL 1 month prior), CO2 19 mmol/L with anion gap 15, and albumin 2.8 g/dL. CBC was within normal limits. Urinalysis showed protein >500, blood 2+, WBC 10/hpf, RBC 53/hpf, nitrite negative, and leukocyte esterase negative. Urine random protein/ creatinine ratio was >6.2. Urine eosinophils were negative. Glomerulonephritis labs included, revealed negative ANCA, ANA 1:80, streptozyme <100, C3 116 mg/dL [80-160 mg/dL], C4 27 mg/dL [16-48 mg/dL], rheumatoid factor <10 IU/mL, hepatitis BsAg nonreactive, hepatitis C antibody nonreactive, HIV-1/2 Ag/Ab nonreactive, and RPR nonreactive.

Renal biopsy showed diffuse IgA-dominant immune complex-mediated glomerulonephritis with focal necrotizing and crescentic lesions most consistent with subacute IgA-dominant post-infectious glomerulonephritis. Moderate arteriosclerosis was also seen.

After pulse steroids, the patient was treated with prednisone 60 mg daily and cyclophosphamide 100mg PO twice daily. During the first month of treatment, the serum creatinine progressively rose to 2.8 mg/dL. Hemodialysis was started, and the patient presented to UCLA for a second opinion and renal transplant evaluation. During the second month of treatment, he developed leukopenia, invasive pulmonary aspergillosis, and CMV viremia, and immunosuppressive treatment was held. Renal function progressively declined and the patient became dependent on hemodialysis. He is now listed for a kidney transplant.

Discussion

This aggressive case of glomerular disease clinically resulted in severe hematuria, rapidly progressive acute kidney injury, and eventual end stage renal disease. The rapidly progressive nature of the glomerular disease evoked two distinct possibilities a crescentic IgA nephropathy (HSP) and IgA dominant PIGN. Severe crescentic IgA nephropathy is a confounding diagnosis that needs to be excluded in acute kidney injury in setting of an infection. Severe crescentic IgA nephropathy can mimic many of findings of post infectious glomerulonephritis.[4,5] C3 glomer-

ulonephritis can be very difficult to distinguish from PIGN pathologically. The main difference is immunofluorescence ratio of immunoglobulin (Ig) to C3 deposits. Generally, for C3GN the C3 to Ig ratio needs to be greater than 2:1.[6] One clue to identify post streptococcal glomerulonephritis and PIGN in general is presence of neutrophilic infiltrates as well as immune complex deposition. PIGN tends to be IgG dominant, though there are cases of other immunoglobulin dominant types.[5] The PIGN IgA dominant pattern is rarer, and has aggressive behavior. The patient was treated aggressively by an outside nephrologist but needed to stop his immunosuppressive therapy due to life threatening infectious complications.

More cases of IgA dominant post infectious glomerulonephritis should be studied to better understand this PIGN variant. For now, the only treatment for rapidly progressive glomerulonephritis is high dose steroids and cyclophosphamide.[7] The risks of non-targeted chemotherapeutic agent include both short term infection, and long term of malignancy, and gonadal failure. Additional study of this pathological entity will be needed before safe and effective alternative treatments are developed.

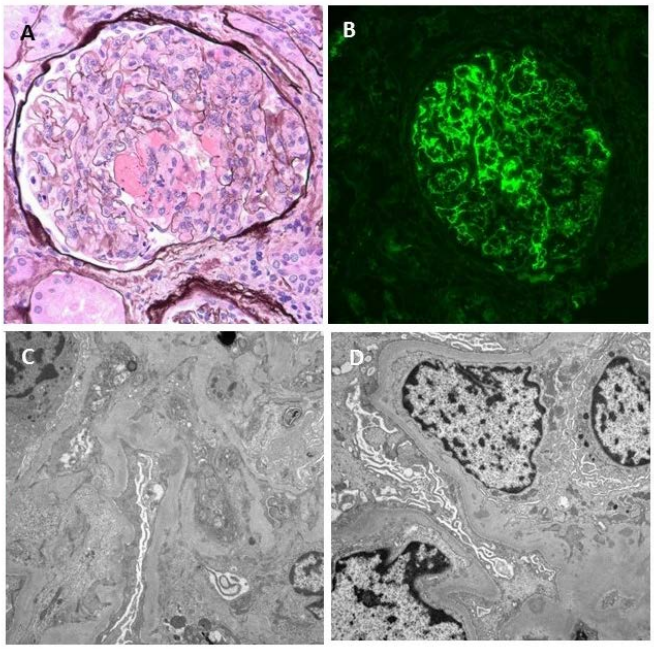

Figure 1: Renal biopsy of patient with IgA dominant PIGN; slides from biopsy obtained from the renal pathology department at Cedars Sinai Medical Center, courtesy of Dr. Jean Hou.

A) Light microscopy 40x, showing neutrophil dominant infiltrate typical of Post Infectious Glomerulonephritis (PIGN) B) Immunofluorescence showing intense IgA staining C-D) Electron microscopy showing subepithelial, subendothelial, and mesangial deposits typical of PIGN

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Submitted August 12, 2018