



IgA-Dominant Acute Postinfectious Glomerulonephritis Presenting as Acute Renal Failure in a Kidney Transplant Recipient

Manish Anand^{1,4}, Juan Pablo Arroyo^{2,4}, Hassan Alhalabi¹, Timothy Thayer², Mark Lusco³, Anthony Langone¹ and Beatrice P. Concepcion¹

¹Division of Nephrology and Hypertension, Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ²Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; and ³Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence: Beatrice P. Concepcion, 1161 21st Avenue South, S-3223 MCN, Nashville, Tennessee 37232, USA. E-mail: beatrice.p.concepcion@vanderbilt.edu

⁴Manish Anand and Juan Pablo Arroyo contributed equally to this work.

Kidney Int Rep (2017) **2**, 766–769; <http://dx.doi.org/10.1016/j.ekir.2017.01.011>

Copyright © 2017, International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

IgA-dominant acute postinfectious glomerulonephritis (APIGN) is a morphologic variant of APIGN in which IgA is the dominant or co-dominant Ig found in glomerular immune deposits. It is a rare disease and, to our knowledge, has not been previously reported in a kidney transplant recipient. Here we describe a case of IgA-dominant APIGN that developed in an immunosuppressed kidney transplant recipient despite appropriate antibiotics and source control of his infection with limb amputation. He presented with severe renal failure after a bout of *Staphylococcus aureus* septicemia. Early biopsy and subsequent recognition of the disease led to empiric steroid therapy that ultimately resulted in renal recovery.

CASE PRESENTATION

A 62-year-old man of white ethnicity with a history of end-stage renal disease (ESRD) presumed to be secondary to diabetes and hypertension had received a deceased donor kidney transplant (1 antigen mismatch, panel-reactive antibodies negative) 4 years previously and was maintained on tacrolimus and mycophenolate mofetil. He presented to the emergency department for evaluation of a tender, erythematous, swollen lesion on the plantar aspect of the right foot. On admission (day 0), the patient had an elevated white blood cell count of $11.6 \times 10^3/\mu\text{l}$, and his creatinine (Cr) value was at his baseline of 1.6 mg/dl (142 $\mu\text{mol/l}$). Initial

imaging of the foot showed osteolysis concerning for osteomyelitis. Incision and drainage was performed at bedside, with purulent drainage obtained, and patient was started on piperacillin-tazobactam and vancomycin. Blood cultures grew methicillin-sensitive *S aureus*, and the patient underwent a below-the-knee amputation with clean surgical margins 48 hours after admission (day 2). Antibiotics were narrowed to nafcillin, repeat blood cultures remained negative, and the patient was discharged to an inpatient rehabilitation facility with a Cr of 1.49 mg/dl (132 $\mu\text{mol/l}$) (day 5).

Records from the inpatient rehabilitation noted a progressive decrease in urine output, which began 2 days after discharge from our facility (days 7–8). The patient was challenged with i.v. fluids and diuretics, with a poor response in urine output. He was then transferred back to our hospital for anuric acute kidney injury (AKI). On readmission (day 12), laboratory studies were significant for a Cr of 8.25 mg/dl (731 $\mu\text{mol/l}$), urinalysis with 2+ protein, 122 white blood cells, and 133 red blood cells, spot urine protein–creatinine ratio of 1.03 g/g, and a urinary sodium <20 mEq/l. Complement 3 (C3) was low (59 ref. 82–193 mg/dl), and complement 4 was normal (21 ref. 15–53 mg/dl). Serum IgA level was normal at 412 mg/dl. Tacrolimus 12-hour trough level was 2.6 ng/ml. Urine culture had no growth. Renal transplant ultrasound showed normal Doppler signal and no hydronephrosis. A renal transplant biopsy was performed approximately 24 hours after readmission (day 13).

The kidney biopsy sample consisted of 3 pieces of cortex and 1 piece of corticomedullary junction containing 10 glomeruli, none of which were globally sclerosed by light microscopy. There was diffuse global glomerular endocapillary hypercellularity with frequent neutrophils, and two glomeruli had fibrinoid necrosis within the glomerular tuft (Figure 1). There was focal mild dilation of proximal tubules with flattening of tubular epithelium that showed loss of brush borders and apical blebbing involving about 20% of tubular profiles. There was no morphologic evidence of acute T-cell or antibody-mediated rejection. By immunofluorescence microscopy, IgA was the dominant Ig, with stronger C3 staining in a diffuse global granular mesangial and irregular chunky capillary loop pattern (Figure 2). There was equal intensity staining for kappa and lambda. By electron microscopy, there were frequent mesangial, scattered subendothelial, and rare subepithelial deposits (Figure 3).

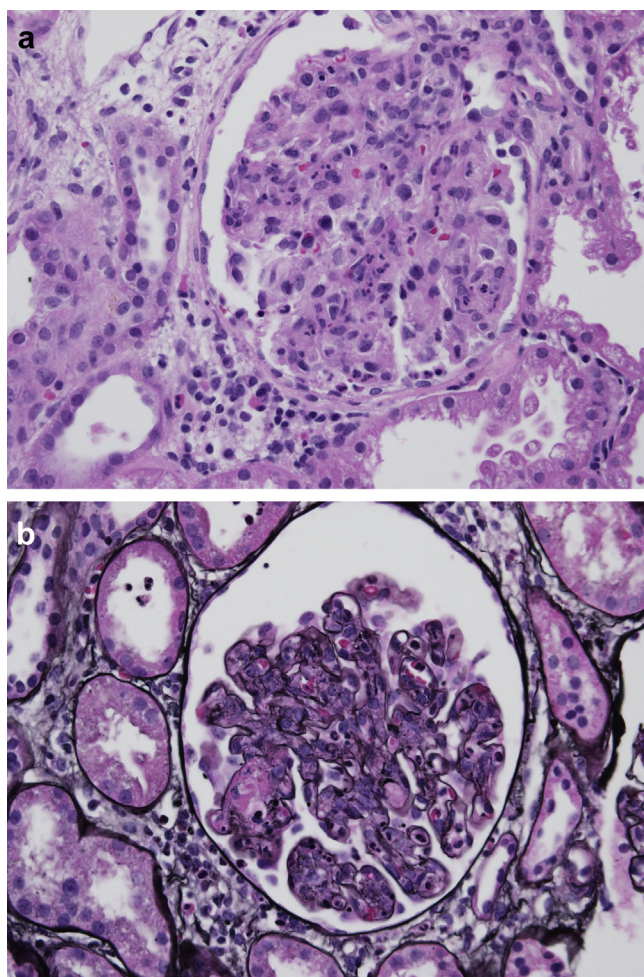


Figure 1. Light microscopy shows a diffuse proliferative immune complex glomerulonephritis characterized by (a) diffuse glomerular endocapillary hypercellularity with frequent neutrophils (hematoxylin and eosin stain). (b) Two glomeruli show fibrinoid necrosis within glomerular capillary loops (Jones silver stain). Original magnification $\times 400$.

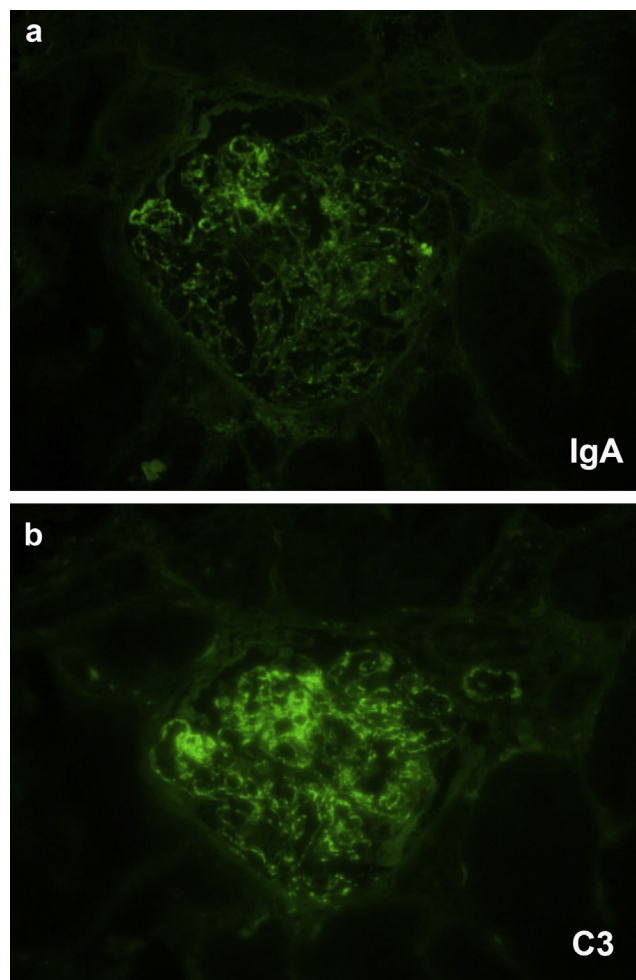


Figure 2. Immunofluorescence microscopy shows (a) dominant IgA Ig with (b) stronger C3 granular and chunky mesangial and irregular capillary loop staining (immunofluorescence microscopy; IgA and C3). Original magnification $\times 400$.

Given the biopsy results, the patient was started on pulse doses of methylprednisolone 500 mg daily for 3 days, then transitioned to prednisone 40 mg daily. Antibiotics were stopped after cultures had no growth and the surgical team believed that the wound was not infected. The patient's renal function improved rapidly, with a daily improvement in Cr as well as urine output. He was subsequently discharged back to the inpatient rehabilitation facility with a Cr of 2.11 mg/dl (187 $\mu\text{mol/l}$). Steroids were tapered over a period of 3 months. On clinic follow-up 5 months after his initial presentation, Cr was 1.7 mg/dl (150 $\mu\text{mol/l}$), urinalysis had 1+ protein, 1 white blood cell, and 18 red blood cells, and spot urine protein–creatinine ratio was 0.3 g/g.

DISCUSSION

IgA-dominant APIGN, a morphologic variant of APIGN, was described by Nasr *et al.* in 2003 in 5 diabetic patients who developed AKI after a staphylococcal infection.¹

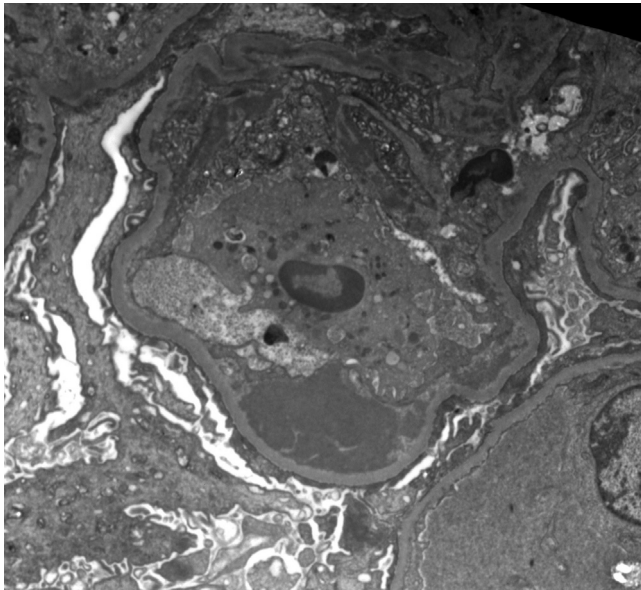


Figure 3. Electron microscopy demonstrates rare subepithelial (not shown), scattered subendothelial, and frequent mesangial deposits. There is an inflammatory cell within the capillary loop (electron microscopy). Original magnification $\times 5600$.

Histologically, light microscopy revealed an acute proliferative and exudative glomerulonephritis similar to classic AIPGN; but on immunofluorescence (IF), IgA was the sole or dominant Ig deposited in glomeruli as opposed to IgG/C3 or C3 alone, which is seen in classic AIPGN. Electron microscopy (EM) showed predominantly mesangial deposits and sparse, small subepithelial deposits, some of which were hump shaped. Haas *et al.*² similarly described a series of 13 patients with IgA-dominant AIPGN in various stages of resolution, all of whom had large, subepithelial, hump-shaped deposits typical of classic AIPGN. In a review by Nasr and D'Agati,³ the authors suggested that to distinguish IgA-dominant AIPGN from primary IgA nephropathy, the diagnostic features of IgA-dominant AIPGN should include endocapillary proliferation, subepithelial deposits, or hypocomplementemia. In a review by Gaut and Liapis⁴ of 64 patients with IgA-dominant AIPGN, the authors similarly used this criterion to distinguish these cases from those of "IgA nephropathy associated with staphylococcal infection,"⁵ in which the above pathologic or laboratory findings of classic AIPGN were absent. In Nasr and D'Agati's review of 49 cases,³ 63% of patients had endocapillary proliferative and exudative glomerulonephritis on light microscopy. On immunofluorescence, all patients had IgA-dominant or IgA-co-dominant Ig staining; most patients had high-intensity staining for C3; and 69% of patients had equal or stronger staining for kappa compared to lambda. On EM, 96% of patients had mesangial electron-dense deposits, and

83% of patients had subepithelial deposits, frequently hump shaped.

Our patient's biopsy findings are consistent with IgA-dominant AIPGN in that there was a diffuse proliferative and exudative glomerulonephritis on light microscopy. On IF there was IgA-dominant Ig staining with stronger C3 staining, which is consistent with previous observations.^{1,3} In addition, kappa and lambda staining were equal in intensity, which is also consistent with previous observations,^{2,3} and IF staining was irregular and chunky, consistent with the "starry sky" pattern that is typical of AIPGN. Unlike the findings of Haas *et al.*,² in which subepithelial deposits were large, numerous, and hump shaped, we were not able to capture such large, hump-shaped, subepithelial deposits on EM. Our findings are therefore more consistent with earlier observations by Nasr *et al.*¹ in that subepithelial deposits in IgA-dominant AIPGN may be small and sparse.

Clinically, patients with IgA-dominant AIPGN typically present with AKI, hematuria, and proteinuria. Hypocomplementemia is a common feature, occurring in 69% of patients.³ In the majority of patients, diabetes mellitus is identified as a significant risk factor. Mean age of presentation is 60 years (range 16–85 years), and males are affected more than females at 3.9:1. An associated staphylococcal infection is identified in a majority of these cases. The mean time from infection to kidney injury is 4 weeks (range 0–16 weeks).³ Our patient shared many of the clinical characteristics described above, including the presentation of AKI with hematuria, proteinuria, and hypocomplementemia, presence of concurrent diabetes, and documented *S aureus* infection within 2 weeks of AKI.

The pathogenic mechanisms responsible for the selective deposition of IgA in patients with post-staphylococcal glomerulonephritis are incompletely understood. A group from Japan described a role of staphylococcal enterotoxins B and C in methicillin-resistant *S aureus*-associated glomerulonephritis.⁶ The enterotoxin acts as a superantigen that binds directly to class II major histocompatibility complex molecules on antigen-presenting cells, thus triggering a massive cell activation and generation of inflammatory cytokines. It leads to polyclonal activation of IgA and IgG, resulting in the formation of IgA and IgG immune complexes. The same group discovered a *S aureus* envelop antigen "probable adhesion" and proposed its role as the antigen for induction of an IgA immune response in IgA nephropathy.⁷

There is no systematic evaluation of treatment options of IgA-dominant AIPGN. Antibiotics to treat the underlying infection are the mainstay. Steroids have been successfully used in a few case reports.⁸ Our

patient received appropriate antibiotics, his infection was well-controlled when he developed AKI, and he had a clinical picture consistent with a rapidly progressive glomerulonephritis. Although no crescents were seen on biopsy, the presence of diffuse endocapillary proliferation and focal fibrinoid necrosis indicated a severe inflammatory process occurring in the allograft. High-dose steroids were initiated for their anticytokine and overall anti-inflammatory effects, and also to potentially attenuate the host interaction with the bacterial superantigen. The patient responded well to this therapy, indicating that there is probably a role for steroids in such a clinical scenario, when there is adequate infection control.

Prognosis in IgA-dominant APIGN is generally poor. In a comprehensive review by Gaut and Liapis,⁴ following treatment with antibiotics or antibiotics plus steroids, 16% of patients (10/63) had a complete recovery, 49% (31/63) showed partial renal dysfunction, and 38% (24/63) developed ESRD. Of the 5 patients who died, 4 developed ESRD prior to death. Marginal renal function prior to disease onset was present in the majority of patients who developed ESRD.

To our knowledge, this is the first reported case of IgA-dominant APIGN occurring in a renal transplant recipient. Of note, there have also been only a few case reports of classic APIGN occurring in this patient population.⁹ This is despite the susceptibility of these immunosuppressed patients to infections. It is possible that there may simply be underrecognition or underreporting of this condition. We speculate, however, that maintenance immunosuppression with drugs such as calcineurin inhibitors or steroids may confer a protective effect against this disease by attenuating the immune response that is generated in APIGN. We suspect that our patient, who was on a steroid-free maintenance regimen and had a 12-hour tacrolimus trough of 2.6 ng/ml on presentation, may have been more susceptible to this disease compared to other transplant recipients due to a relatively low level of immunosuppression.

This case report highlights the importance of increased awareness among transplant physicians for this disease entity. Sepsis with subsequent AKI is not uncommon in renal transplant patients and, in a majority of cases, can easily be attributed to acute tubular necrosis from sepsis itself, ischemic injury from hypotension, or a pre-renal etiology from volume depletion. At times, antibiotics may be thought of as the culprit, due to either direct nephrotoxicity or acute interstitial nephritis. However, in the appropriate clinical setting in which a

patient has a recent history of staphylococcal infection and develops AKI with a corresponding active urine sediment, early biopsy is warranted to ascertain a cause, including an evaluation for IgA-dominant APIGN. This includes IF and EM evaluation of the renal biopsy specimen. Physicians who are not clinically suspicious of IgA-dominant APIGN may delay performing a biopsy in favor of conservative management such as i.v. fluids or discontinuation of culprit antibiotics. In this case, early biopsy led to a prompt diagnosis and successful intervention.

In summary, IgA-dominant APIGN may occur in the renal allograft. Recognition of this disease entity is an important first step in determining appropriate management. Steroids may have a therapeutic role in cases in which renal function continues to deteriorate despite appropriate antibiotics and source control of the infection. Further studies are warranted to determine the optimal treatment regimen in such cases, including dose and duration of therapy.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Nasr SH, Markowitz GS, Whelan JD, et al. IgA-dominant acute poststaphylococcal glomerulonephritis complicating diabetic nephropathy. *Hum Pathol.* 2003;34:1235–1241.
2. Haas M, Racusen LC, Bagnasco SM. IgA-dominant post-infectious glomerulonephritis: a report of 13 cases with common ultrastructural features. *Hum Pathol.* 2008;39:1309–1316.
3. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clin Pract.* 2011;119:c18–c25 [discussion: c26].
4. Gaut JP, Liapis H. IgA dominant post-infectious glomerulonephritis: pathology and insights into disease mechanisms. *Diagn Histopathol.* 2013;19:175–181.
5. Satoskar AA, Nadasdy G, Plaza JA, et al. Staphylococcus infection-associated glomerulonephritis mimicking IgA nephropathy. *Clin J Am Soc Nephrol.* 2006;1:1179–1186.
6. Koyama A, Kobayashi M, Yamaguchi N, et al. Glomerulonephritis associated with MRSA infection: a possible role of bacterial superantigen. *Kidney Int.* 1995;47:207–216.
7. Kai H, Shimizu Y, Hagiwara M, et al. Post-MRSA infection glomerulonephritis with marked *Staphylococcus aureus* cell envelope antigen deposition in glomeruli. *J Nephrol.* 2006;19:215–219.
8. Kapadia AS, Panda M, Fogo AB. Postinfectious glomerulonephritis: is there a role for steroids? *Indian J Nephrol.* 2011;21:116–119.
9. Moroni G, Papaccioli D, Banfi G, et al. Acute post-bacterial glomerulonephritis in renal transplant patients: description of three cases and review of the literature. *Am J Transplant.* 2004;4:132–136.