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Crescentic glomerulonephritis in renal transplant; a case series

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ABSTRACT

Crescentic glomerulonephritis (GN) is a severe proliferative renal lesion with an aggressive clinical scenario. The occurrence of crescentic GN post-transplant is mainly related to the recurrence of the primary glomerular disease. De novo crescentic GN in renal allografts is rare. We present five patients diagnosed with crescentic GN post-transplantation during 10 years period. There were two males and three females with age range 20-50 years. Three cases were crescentic phenotypes of recurrent disease and two were de novo. The post-transplant time range was (7-144 months). Three patients lost their grafts and returned to dialysis. One patient had chronic allograft dysfunction and one patient died because of severe renal failure. Recurrent or de novo crescentic GN is not uncommon, especially in a live donor program. It leads to graft loss in most cases.

Implication for health policy/practice/research/medical education:

Crescentic glomerulonephritis in a renal allograft should be always considered. Albeit uncommon but it is a serious cause of graft loss and patient mortality.

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Introduction

Since the first mention by Volhard and Fahr in 1914, renal crescents represented the histologic marker of severe glomerular injury and aggressive clinical disease (1).

Crescent is the result of an extracapillary hypercellularity other than epithelial hyperplasia of the collapsing variant of focal segmental glomerulosclerosis (FSGS), often accompanied by fibrin extravasation into Bowman's space (2).

Crescentic glomerulonephritis (GN) is typically associated with the syndrome of rapidly progressive GN, which can occur in most forms of inflammatory glomerular injury, including postinfectious GN, IgA nephropathy (IgAN), lupus nephritis, renal vasculitis, membranoproliferative GN, and anti-glomerular basement membrane (GBM) antibody disease (3).

It is well-known that GN may recur after kidney transplantation, with reported rates varying widely, from 2.6% to 50% in previous studies. In a Korean study, the incidence rate of GN post-transplant was 9.7% and 17.0% at 5 and 10 years of follow-up, respectively (4).

De novo GN is reportedly uncommon (5,6). The rate of recurrence of primary disease determines the rate of the crescentic lesion but de novo crescentic GN seems to be very rare.

ANCA associated vasculitis (AAV), IgA nephropathy, and lupus nephritis are the most common causes of crescentic GN post-transplant. Other causes include infections, drug-induced, membranoproliferative GN (MPGN), anti-GBM antibody disease (anti-GBM disease), and monoclonal gammopathies (7).

We failed to find data about the distinct title of "crescentic glomerulonephritis in a renal transplant" except a single report in 1990 (8).

Here, we will present a series of five cases of post-transplant crescentic GN that have been recorded in our unit for over 10 years (Table 1).

Patients and Methods

A total of 567 renal transplants were performed in the nephrology and renal transplantation center, the medical city, Baghdad from January 1, 2009, to December 31,

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Table 1. The clinical data of the case series

	Gender	Age	Recurrent /De Novo	Primary / De Novo Disease	Time Post-Tx	Outcome
Patient 1	Male	34	Recurrent	MPGN/ C3GN	7 months	HD
Patient 2	Male	21	Recurrent	IgAN	1.5 years	Death
Patient 3	Female	20	Recurrent	Lupus nephritis	4 years	HD
Patient 4	Female	49	De Novo	ANCA - vasculitis	12 years	HD
Patient 5	Female	50	De Novo	MGRS/ LCDD	3.5 years	Graft dysfunction

MPGN; Membranoproliferative glomerulonephritis, C3GN; Complement 3 glomerulonephritis, HD; hemodialysis, IgAN; Immunoglobulin A nephropathy, MGRS; Monoclonal gammopathy of renal significance, LCDD; Light chain deposition disease.

2019. It is a live donor blood group compatible program. Allograft biopsy performed per cause and the minority had protocol biopsies. We reviewed all patients' data and specifically looked for crescentic GN on pathology reports. Five cases were recorded (0.88%). Retrospective analysis for the therapeutic intervention and outcomes was done. All reported patients in this series were induced with basiliximab and maintained on triple therapy (calcineurin inhibitors, mycophenolic acid, and steroids).

As part of the diagnostic workup, all patients were tested for connective tissue and viral serology, complements, plasma and urine light chains, and renal imaging. Patients with de novo forms were screened for malignancy.

Case 1

A 34 years old male with chronic GN and membranoproliferative pattern had a live donor transplant from his wife. He kept excellent graft function with a creatinine of 1 mg/dL at 6 months post-transplant. He suddenly presented with acute graft dysfunction and a creatinine of 4.3 mg/dL, proteinuria (5 g per day), hematuria, and red cell casts. Renal allograft biopsy revealed a membranoproliferative pattern with crescent formation (Figure 1). Staining for C4d was negative however we saw a diffuse C3 deposit. Staining for IgG, IgA, IgM, kappa, and lambda were negative. The serum complement level shows low C3. The histopathology report suggested recurrent complement 3 GN (C3GN). Testing for alternative pathways and electron microscopy is not available. He received pulse steroid, dialysis, and plasma exchange with a futile response as he returned to dialysis.

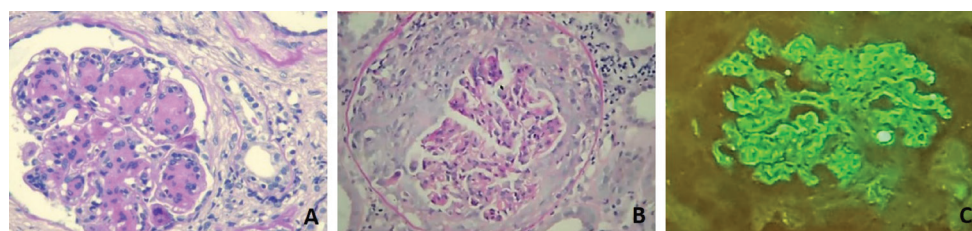


Figure 1. Hematoxylin and eosin stain (A) Lobulated pattern of MPGN, (B) Crescent, and (C) Diffuse C3 staining on IF.

Case 2

A 21 years old male with IgA nephropathy and positive family history underwent renal transplantation from a live unrelated donor in February 2016. His serum creatinine at 12 months was 1.1 mg/dL. On 18 months post-transplant, he presented with frank hematuria and 5 gm/day urine protein excretion and acute kidney injury (AKI). His serum creatinine was 6 mg/dL. Renal biopsy revealed crescentic GN with IgA mesangial deposits which confirmed the recurrence of the original disease however no rejection was detected (Figure 2). Hemodialysis was initiated as well as methylprednisolone pulse and IV cyclophosphamide. He rapidly deteriorated with acute heart failure and unfortunately died with severe renal failure and acute heart failure.

Case 3

A 20 years old female with lupus nephritis had renal transplantation in 2012. Her serum creatinine at one year was 1 mg/dL. In 2014, she presented with new-onset proteinuria with normal renal function. She refused

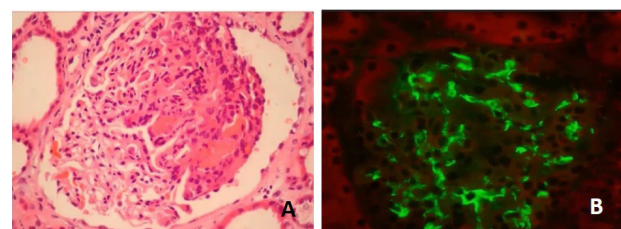


Figure 2. Hematoxylin and eosin stain (A) Crescentic IgA and (B) Diffuse mesangial IgA deposit on IF.

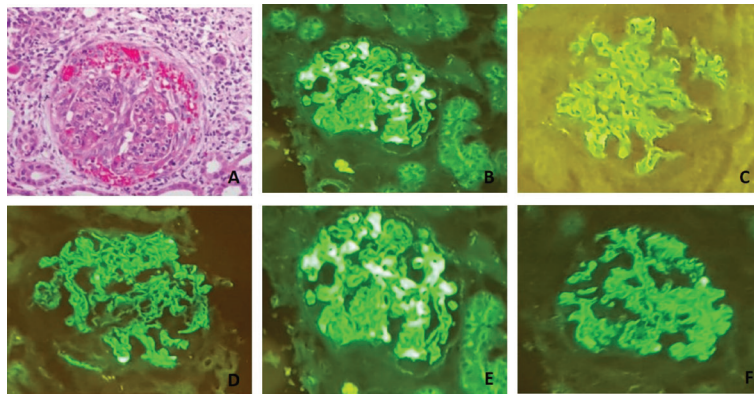


Figure 3. Hematoxylin and eosin stain (A) Crescentic LN, with full house immune deposit on IF (B) IgG, (C) IgM, (D) IgA, (E) C3, and (F) C1q.

renal allograft biopsy conduction. Accordingly, her immunosuppression and antiproteinuric measures were optimized with the addition of hydroxychloroquine. Lupus serology at that time was inconclusive with only positive antinuclear antibody (ANA) since there was a hypocomplementemia. In 2016, she presented with edema, hematuria, and proteinuria and serum creatinine of 4 mg/dL. Allograft biopsy revealed diffuse proliferative (class IV) crescentic lupus nephritis and full house pattern on immunofluorescence (IF) (Figure 3). She received pulse steroids and cyclophosphamide, while she became dialysis dependent four months later.

Case 4

A 49 years old lady with non-proteinuric end-stage renal disease (ESRD) underwent a renal transplant in 2006. In 2010 she had proteinuria with a normal serum

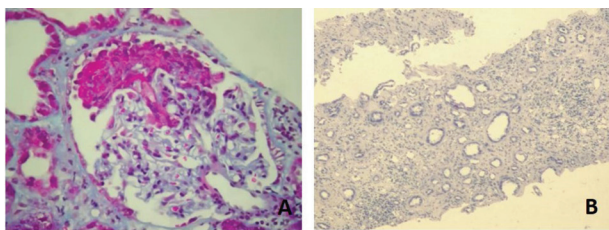


Figure 4. Masson trichrome stain (A) Crescent with glomerular necrosis in a pauci-immune GN, and (B) IF/TA >20%.

creatinine. Renal biopsy showed nonspecific changes and 20% interstitial fibrosis and tubular atrophy (IF/TA) however, no rejection that mandated optimization of immune suppression. In 2018, she presented with AKI, serum creatinine was 6 mg/dL; hematuria, and 3 gm of urinary protein over 24 hours were detected too. Renal biopsy revealed a fibrocellular crescent on the background of IF/TA (Figure 4). All serology was negative except for positive C-ANCA of 1:160 titer. There were no other clinical signs and no vasculitic rashes. She received steroid pluses and cyclophosphamide while hemodialysis started. She had remained dialysis-dependent.

Case 5

A 50 years old lady with LUD transplant in 2015 for hypertensive nephrosclerosis. She had an excellent graft function at one year with a creatinine of 0.9 mg/dL. By 18 months post-transplant, she developed new-onset diabetes mellitus after transplantation and kept on oral therapy with acceptable control. In June 2018 she presented with volume overload and AKI. Serum creatinine doubled to 1.8 and abruptly escalated to 5 mg/dL over 3 weeks. Additionally, there was 6 gm of protein in urine with hematuria and active urine sediments. Renal biopsy (Figure 5) showed crescentic GN with kappa light chain deposits on IF and no evidence of rejection. Bone marrow

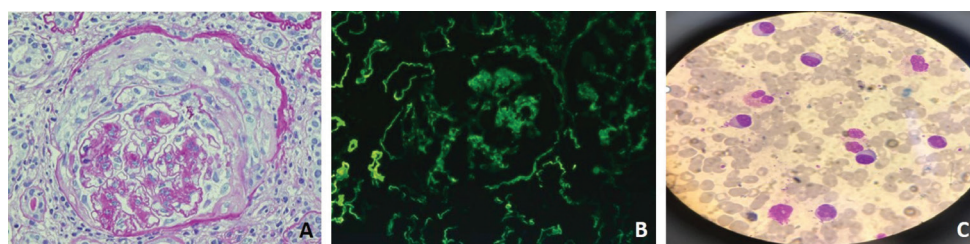


Figure 5. (A) PAS stain with crescent, (B) positive kappa deposition on glomerular and tubular basement membranes, and (C) plasma cells in the bone marrow <20%.

study and CD138 immunohistochemical stain revealed <5% plasma cells with Kappa light chain restriction. There were no detectable monoclonal paraproteins on serum and urine electrophoresis. PET-CT scan was negative. Her serum free light chain assay showed (Kappa 129.7 mg/L and Lambda 24 mg/L) with a reversed ratio of 5.51 which is consistent with the light chain deposition disease (LCDD) diagnosis on biopsy. She started hemodialysis and bortezomib-based therapy initiated. She received hemodialysis (HD) therapy for three months. Now, 2 years after treatment, her serum creatinine is 1.9 mg/dL, with no evidence of plasma cells on bone marrow but still positive urine testing for the light chain.

Discussion

The true prevalence of recurrent and de novo glomerular diseases cannot be calculated correctly for different reasons. Patients usually present late and some cases may go unrecognized. Physicians may be reluctant to have a biopsy diagnosis or may relate proteinuria to allograft dysfunction (9). Using PubMed and Google Scholar search engines, we failed to find Arab and regional data about this issue. The recently established Iraqi renal transplant registry may add Iraqi data in the future.

When compared with other MPGN patterns, C3GN tends to recur at higher rates, 70%. It generally presents within 1-2 years after transplantation and they run an aggressive course with a high risk of allograft failure of around 50% (10). This is compatible with our patient's presentation and outcome (case 1).

IgA nephropathy (IgAN) is the commonest recurrent GN after kidney transplantation. It appears that the male gender is a risk for crescentic GN in native kidneys. The greater the number of crescentic glomeruli in native kidney, the more risk of recurrence. The mean rate of IgA recurrence is 33% (11). Some histologic recurrences are not clinically relevant. Rapidly progressive GN and crescentic presentation usually lead to allograft loss. Crescentic IgA nephropathy may recur in consecutive transplants as in the report by Gopalakrishnan et al (12). IgAN may recur in the same transplant but with different phenotypes. It may be just a mesangial deposit and proliferation with proteinuria at first and then a crescentic pattern (12,13). Intravenous cyclophosphamide is recommended for rapidly progressive crescentic IgAN in native kidneys by KDIGO guidelines (14). This is largely unproven and unlikely to successfully reverse the disease process in aggressive recurrent disease. A recent report suggested that insulin-like growth factor-1 may play a role in mesangial cell proliferation in IgAN and somatostatin may inhibit insulin-like growth factor-1. Thus octreotide, a somatostatin analog, is used as a potential novel therapy for early recurrent IgAN post kidney transplant.

Published literature has shown an increased expression of somatostatin receptors in kidney tissue of patients with IgAN, suggesting a possible role in the pathogenesis of IgAN (15).

Recurrent lupus nephritis is a big concern in transplant patients with ESRD secondary to lupus nephritis (LN). It can recur days to years after transplantation with a variable rate, up to 54%. Young female, African American ancestry, and antiphospholipid antibodies carry a high risk of recurrence (16). The patient in case 3 was a young female with positive antiphospholipid antibodies. Most of the patients who present with clinical recurrence had diffuse proliferative GN on biopsy. Severe lupus flare with a rapid decline in renal function and crescentic GN, merits aggressive treatment with pulse steroid, increasing doses of mycophenolate mofetil, initiation of cyclophosphamide, or rituximab. Still, 7% of patients with recurrent lupus nephritis will develop graft failure and those were mostly the cases with aggressive clinical and histological phenotypes (16,17).

Pauci-immune crescentic GN is the most common cause of rapidly progressive renal failure. The majority of cases are associated with the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) with a specificity of 99.3% and a wide range of sensitivity (34%–92%). In the 2007 single-center study by Gera et al, recurrence of AAV occurred in 9% presented > 1.5 years post-transplant (18). De novo AAV rarely occurs with few case reports. Patients usually present years after transplantation as in our patient, case 4, who presented 6 years after transplantation (19).

LCDD has a very high rate of recurrence but de novo LCDD is very rare in kidney transplant recipients. Ecker et al reported a case of de novo LCDD without evidence of malignancy 16 years after deceased donor transplantation (20). It was a kappa light chain disease as in our patient, case 5 (21). Whether recurrent or de novo, LCDD frequently leads to graft failure.

In a live donor program like ours, we should not overlook the notion that living donation may be considered as a risk factor for the recurrence of glomerular disease post-transplant. Deng et al reported an increased risk of FSGS and IgAN recurrence among live-related donors. Living donation is also associated with a high risk of LN recurrence (22).

All patients in this series received induction therapy with basiliximab. During the period from 2009 to 2019, about 30% of our patients induced with antithymocyte globulin. We did not find data about the relation between induction agents and the risk of glomerular disease recurrence post-transplant. The introduction of newer immunosuppressive agents and induction protocols improved graft survival. The improvement of graft

survival was through the direct reduction of the incidence of acute rejection. The incidence of posttransplant GN whether recurrence or de novo was not influenced (23).

Conclusion

Recurrent or de novo crescentic GN is not uncommon, especially in a live donor program. It leads to graft loss in most cases.

Authors' contribution

ASA and HAA designed and performed the research. TJK collected the histological data. ASA and HAA analyzed the data. AA wrote the manuscript. All authors reviewed, edited and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. According to the Iraqi research ethics code 2018, institution agreement was taken to review data and use it.

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References

- Heidland A, Gerabek W, Sebekova K, Franz Volhard and Theodor Fahr: achievements and controversies in their research in renal disease and hypertension. *J Hum Hypertens.* 2001;15(1):5-16. doi: 10.1038/sj.jhh.1001130
- Jennette JC, Silva FG, Olson JL, D'Agati VD. Primer on the Pathologic Classification and Diagnosis of Kidney Disease. In: J. Jennette JC, Silva FG, Olson JL, D'Agati VD. *Heptinstall's Pathology of the Kidney*. Seventh edition. Philadelphia, United States: Lippincott Williams and Wilkins; 2014. p. 92-119.
- Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis.* 1988;11:449. doi: 10.1016/s0272-6386(88)80079-9
- An JN, Lee JP, Oh YJ, Oh YK, Ha JW, Chae DW, et al. Incidence of post-transplant glomerulonephritis and its impact on graft outcome. *Kidney Res Clin Pract.* 2012;31(4):219-26. doi: 10.1016/j.krcp.2012.09.004.
- Allen PJ, Chadban SJ, Craig JC, Lim WH, Allen RDM, Clayton PA, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int.* 2017;92(2):461-9. doi: 10.1016/j.kint.2017.03.015.
- Abbas F, El Kossi M, Jin JK, Sharma A, Halawa A. De novo glomerular diseases after renal transplantation: How is it different from recurrent glomerular diseases? *World J Transplant.* 2017;7(6):285-300. doi: 10.5500/wjt.v7.i6.285
- Chen S, Tang Z, Xiang H, Li X, Chen H, Zhang H, et al. Etiology and outcome of crescentic glomerulonephritis from a single center in China: a 10-year review. *Am J Kidney Dis.* 2016;67(3):376-83. doi: 10.1053/j.ajkd.2015.07.034.
- Jones B, Trevillian P, Hibberd A, White K. De novo crescentic glomerulonephritis in a renal transplant. *Am J Kidney Dis.* 1990;16(5):501-3. doi: 10.1016/s0272-6386(12)80068-0
- Dube GK, Cohen DJ. Recurrent and de novo diseases after renal transplantation. In: Weir MR, Lerma EV. *Kidney transplantation. Practical Guide to Management*. New York: Springer; 2014. p.159-172.
- Zand L, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, Gandhi MJ, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. *J Am Soc Nephrol.* 2014;25(5):1110-7. doi: 10.1681/ASN.2013070715.
- Avasare RS, Rosenstiel PE, Zaky ZS, Tsapepas DS, Appel GB, Markowitz GS, et al. Predicting post-transplant recurrence of IgA nephropathy: the importance of crescents. *Am J Nephrol.* 2017;45(2):99-106. doi: 10.1159/000453081.
- Gopalakrishnan N, Muruganath S, Dineshkumar T, Dhanapriya J, Sakthirajan R, Balasubramanian T. Two consecutive recurrences of crescentic immunoglobulin A nephropathy in a renal transplant recipient. *Indian J Nephrol* 2016;26:376-8. doi: 10.4103/0971-4065.169565.
- Soler MJ, Mir M, Rodriguez E, Orfila A, Munne A, Vázquez S, et al. Recurrence of IgA nephropathy and Henoch-Schönlein purpura after kidney transplantation: risk factors and graft survival. *Transplant Proc.* 2005;37(9):3705-9. doi: 10.1016/j.transproceed.2005.09.172.
- Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide) lines—application to the individual patient. *Kidney Int.* 2012;82(8):840-56. doi: 10.1038/ki.2012.280.
- Sharma A, Hariharan S. Octreotide delaying the progression of recurrent iga nephropathy after kidney transplantation. *Transplant Direct.* 2019;6(1):e518. doi: 10.1097/TXD.0000000000000963.
- Burgos PI, Perkins EL, Pons-Estel GJ, Kendrick SA, Liu JM, Kendrick WT, et al. Risk factors and impact of recurrent lupus nephritis in patients with systemic lupus erythematosus undergoing renal transplantation: data from a single US institution. *Arthritis Rheum.* 2009;60(9):2757-66. doi: 10.1002/art.24776.
- Ponticelli C, Moroni G, Glassock RJ. Recurrence of secondary glomerular disease after renal transplantation. *Clin J Am Soc Nephrol.* 2011;6(5):1214-21. doi: 10.2215/CJN.09381010.
- Gera M, Griffin MD, Specks U, Leung N, Stegall MD, Fervenza FC. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosuppression. *Kidney Int.* 2007;71(12):1296-301. doi: 10.1038/sj.ki.5002244.
- Asif A, Toral C, Diego J, Miller J, Roth D. De novo ANCA-associated vasculitis occurring 14 years after kidney transplantation. *Am J Kidney Dis.* 2000;35(3):E10. doi: 10.1016/s0272-6386(00)70222-8
- Ecder T, Tbakhi A, Braun WE, Tubbs RR, Myles J, McMahon JT. De novo light-chain deposition disease in a cadaver

- renal allograft. *Am J Kidney Dis.* 1996;28(3):461-465. doi: 10.1016/s0272-6386(96)90508-9.
21. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis.* 2004;43(1):147-53. doi: 10.1053/j.ajkd.2003.09.020.
 22. Deng R, Dai Y, Zhang H, Liu L, Li J, Xiong Y, et al. Higher Incidence of Renal Allograft Glomerulonephritis in Living-Related Donor Kidney Transplantation. *Transplant Proc.* 2018;50(8):2421-5. doi: 10.1016/j.transproceed.2018.03.050.
 23. Hariharan S, Johnson C, Bresnahan B, Taranto S, McIntosh M, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med.* 2000;342:605-12.

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