C3-Dominant Infection Related Crescentic Glomerulonephritis

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ABSTRACT
Infection related glomerulonephritis and more specifically streptococcal glomerulonephritis is a rare disease in adults, and so is C3 glomerulonephritis. It has been recognized that a clinical and morphological overlap between these two entities exists. We present a case of a 59-year-old man with previous treated HIV infection with virological response, treated hepatitis b infection, treated syphilis and non-Hodgkin lymphoma in remission; presenting and acute sore throat with high ASO titers two weeks before a rapidly progressive glomerulonephritis requiring dialysis since presentation; biopsy showed acute diffuse and proliferative glomerulonephritis with crescentic pattern with exclusive C3 staining. It was considered an acute crescentic glomerulonephritis meeting criteria for infection related glomerulonephritis but also had criteria for C3 glomerulonephritis.

KEYWORDS: infection-related glomerulonephritis, C3 dominant glomerulonephritis, crescentic glomerulonephritis

Introduction

Infection related glomerulonephritis is a low prevalence disease in adult patients, as it is C3 glomerulopathy. It has been recognized that an overlap among these two entities in clinical presentation and histological morphology exists. Here we present a clinical case of a 59-year-old man, with previous history of HIV infection, hepatitis B coinfection, previous syphilis infection and two years later a non-Hodgkin lymphoma; all of them controlled under treatment in case of infections and in remission in the case of lymphoma. The patient presented with sore throat, elevated ASO titers, and two weeks later an acute rapidly progressive nephritic syndrome that required renal replacement therapy; kidney biopsy showed a diffuse exudative proliferative glomerulonephritis with crescents in 55% of glomeruli with immunofluorescence (IF) positive exclusively for C3 staining. It was concluded to be a crescentic C3 dominant postinfectious glomerulonephritis.
In 2008 Nasr et al. [1] in a series of 86 adult patients, proposed 5 criteria to classify an infection related glomerulonephritis (IRGN). These were: 1) clinical or laboratory evidence of recent infection, 2) low C3 complement level, 3) light microscopy showing diffuse proliferative and exudative glomerulonephritis, 4) C3 staining exclusive or dominant to C3 and 5) “humps” images in electronic microscopy. In 2013 a consensus group proposed a new way to classify C3 glomerulopathy (C3G) based on IF and defined it as a positive staining in two or more orders of magnitude of C3 positivity over any other staining [2].

If we analyze these two definitions, there is an overlap between them, and an increasing body of evidence shows this overlap [3, 4]. Besides, it is accepted that one of the recognized causes of C3G is IRGN. Here we present a clinical case of an adult patient with multiple chronic diseases who presents with acute throat infection and demonstration of recent contact with streptococcus species as marked by high ASO titers and a kidney biopsy with showing an infection related glomerulonephritis pattern with crescentic presentation and who required renal replacement therapy due to disease severity, the biopsy also met the proposed criteria for C3G.

Below we present this clinical case of a tertiary care hospital in Colombia, that describes an infrequent presentation of a low frequency disease to enrich the literature about it and put the attention on C3G and IRGN intertwining.

Case Description

This is a 59-year-old male patient, with 26 years history of HIV infection now under high active antiretroviral therapy and recent negative viral load and normal blood CD4+ cells count, previous non-Hodgkin lymphoma 13 year earlier in sustained remission, also previous syphilis infection already treated, brain toxoplasmosis and lung tuberculosis about 5 years earlier, both treated, other morbid conditions were prediabetes and level I obesity. This patient arrives at the hospital with two weeks history of sore throat, malaise, and high blood pressure; two days before the arrival he had macroscopic hematuria that self-relieved. He only took antihistamine drugs, and the symptoms passed. But after hematuria stopped, he began with low appetite, malaise again, and two diarrhea episodes. Laboratory tests showed anemia, elevated creatinine and urine test with proteinuria and hematuria with previous normal creatinine one month earlier, that allowed us to build a diagnosis of rapidly progressive glomerulonephritis. We decided to begin with high dose intravenous steroids and required renal replacement therapy (RRT). Extensive laboratory and image results revealed normal kidneys by ultrasonography, non-nephrotic proteinuria, infectious and autoimmunity laboratories were all normal (Table 1) including serum complement and ASO titers were four times normal level.

Peripheral blood smear	Low erythrocyte count, slight hypochromia and polychromatophilia, microcytosis +, no poikilocytosis
Infectious serologies	HBsAg 0.26 (Negative) Hepatitis C antibodies (Ab) 0.23 (Negative) Hepatitis B anticore Ab 0.4 (Negative) IGM Citomegalovirus Ab 0.4 (Negative)
Immunological	Negative IF anti neutrophil cytoplasm antibodies Anti Myeloperoxidase Ab 2.6 U/mL (ref. below 5) Anti proteinase 3 Ab 3 U/mL (ref. below 12) DNA antibody test negative ANA test negative Anti glomerular basement membrane Ab: 7.0 U/mL negative No monoclonal bands by immunofixation C3 114.9 mg/dL (Ref. 81 – 185) C4 17.7 mg/dL (Ref. 15 – 53) ASO titers 800 UI/mL (Ref. 0-200)
Urine test	Density 1016 pH 5,5 Protein 100 mg/dL Blood cells 760 per HPF Leucocytes 5 per HPF No cast 24-hour protein count: 1370 mg
Blood chemistry	Complete Blood count: white cells 7620/mm^3 Hemoglobin 10,98 gr/dL, platelets 179000/mm^3 Creatinine 10,96 mg/dL BUN 101 mg/dL

Table 1. Infectious, immunological and blood chemistry test at patient arrival.

Kidney biopsy result which had and optimal sample with 20 glomeruli, is described in figure 1.

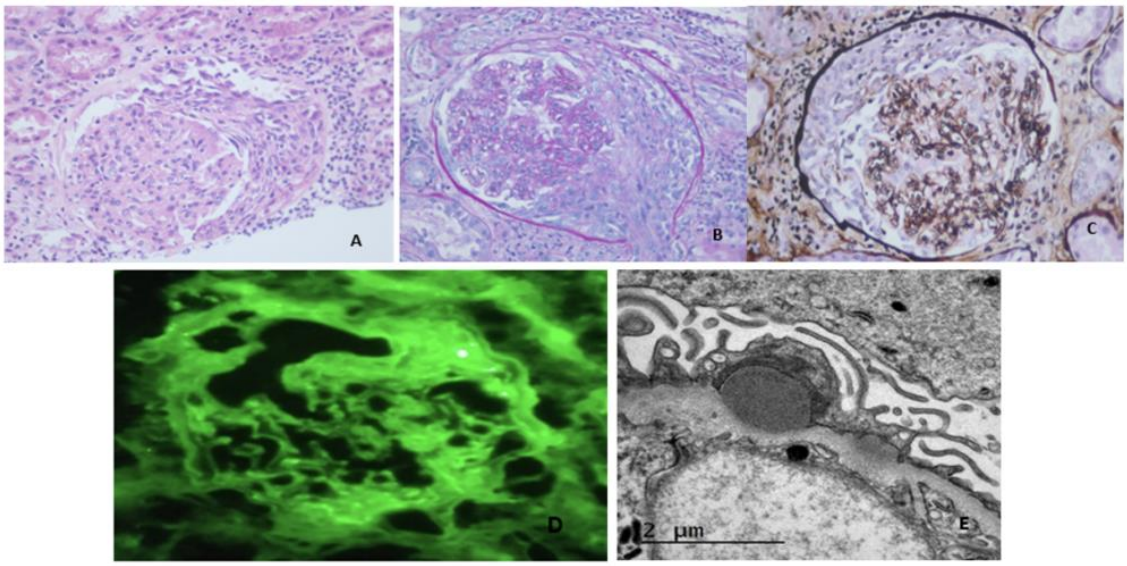

Figure 1. A) H&E 40X shows a glomerulus with mesangial and endocapillary proliferation. 55% of glomeruli with cellular stage crescents. B and C) PAS and silver stain respectively 40X: confirms extracellular proliferation in cellular phase with Bowman's capsule rupture. D) Immunofluorescence with intense C3 staining (+++) in mesangium ang glomerular basement membrane. E) Transmission electron micrography with the presence of electron dense deposits in the subepithelial space with "humps" morphology.

Based on clinical information, laboratory findings, and the biopsy report, a diagnosis of infection-related glomerulonephritis (post-streptococcal glomerulonephritis) with a crescentic presentation and C3-dominant staining was made. The patient went home requiring dialysis and continuing oral prednisone treatment for up to 8 weeks and afterwards withdrawal. Three months later, he got to be free of dialysis with a basal creatinine of 2 mg/dL. In the absence of antibodies to complement proteins in our health system, genetic study with NGS panel with 22 genes for the complement pathway was done, which was totally normal.

Discussion

Streptococcal related glomerulonephritis in adult patients is a rare disease in western countries and is characterized by immune mediated lesion in response to acute serum antigenemia [5, 6]. Studies in patients older than 15 years, between 1988 and 2000, including Hispanic population, estimated an incidence of 2 cases per 100.000 person-years in developing countries and as low as 0.3 cases per 100.000 person-years in developed countries [5, 7]. The male/female ratio ranges from 1.4 to 3 and there are risk factors like immunosuppression, diabetes, older age, alcohol consumption, cancer, malnutrition, intravenous drug use and tuberculosis [5–7]. Most frequent antigens related to pathophysiology of disease are glyceraldehyde-3-phosphate dehydrogenase and bacterial pyrogen endotoxin [6, 7], which are involved in complement activation and consumption, mainly in mesangium and subepithelial basement membrane; these antigens are also related to molecular mimicry or in situ immune complex assembly with previously trapped bacterial antigens. In this process all complement pathways have been implicated. C3 and C5 activation promotes neutrophil chemotaxis and plasmin activation degrading basement membrane and increasing inflammation.

Clinical picture can rarely be asymptomatic and more frequently an acute nephritic syndrome, but less than 5% of cases present with rapid renal function deterioration as in the clinical case presented here. There are many risk factors already mentioned such as immunosuppression and diabetes, that were no present in our patient, whose chronic diseases were well controlled at the time of nephritic syndrome presentation [1, 3, 8, 9].

The presence of high ASO titers in our patient is evidence of recent streptococcal infection but does not predict a specific nephritogenic strain [8, 9]. Hypocomplementemia is also a frequent finding; however, as in our case, 15% to 30% of cases have normal serum complement [1, 3, 8, 9]. Regarding treatment, the KDIGO 2023 guidelines state that nephritis complications, such as hypertension and edema, should be managed, and they recommend a low-salt diet and antibiotic therapy for infections. However, they do not provide clear guidance on the benefits of steroid treatment. Retrospective evidence suggests that steroids do not provide any additional benefit, but data on adults are lacking, and severe cases like ours are rarely included in these series [10].

In our case, due to the absence of immunosuppression from well-controlled HIV infection and the severity of renal impairment, corticosteroids were administered. This is because KDIGO guidelines state that no benefit has been proven from steroids but do not state the weak evidence in severe cases and a lot of case and case series and many authors, in the absence of evidence in these severe crescentic cases, offer steroids to their patients. Our group considered that such a severe case of an immune-mediated disease, with an acute process observed in the biopsy and the need for dialysis, warranted more than just supportive treatment. Therefore, we decided to offer steroid therapy.

Prognosis is usually obscure as 54% of patients present with renal disfunction and 33% of them progress to end stage renal disease in the long term [1, 3, 8, 9] but other comorbid conditions are associated with these outcomes, as previous diabetes. Besides, in our view, the presence of C3-dominant staining and the biopsy morphology fulfill the definition of C3GN. Therefore, abnormalities in the alternative complement pathway should be ruled out. However, the best scenario for suspecting primary complement abnormalities remains the so-called atypical IRGN, in which permanent complement consumption is present. In our case, this was not observed, as complement levels were normal.

An interesting tool is C4d staining, where positivity indicates classical pathway activation. Therefore, negative staining would support alternative complement pathway activation, as suggested by some studies. In our case, C4d staining was negative [11, 12]. If a complement pathway anomaly remains suspected, the next step is to investigate the alternative pathway. Unfortunately, we do not have

tests for nephritic factors or specific antibodies. Additionally, genetic complement studies — which usually have a success rate of around 20% — had not been performed at the time of this publication due to the patient's choice [13].

Conclusion

We present an infrequent crescentic presentation of streptococcal IRGN in an adult with an exclusive C3 staining posing the probability of a C3 glomerulonephritis favored by streptococcal infection. There is a need for more evidence to differentiate these two overlapping diseases with different etiopathogenic backgrounds, different prognosis and even different treatment, and more description about outcome related factors.

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BIBLIOGRAPHY

1. Nasr SH, Markowitz GS, Stokes MB, Said SM, Valeri AM, D'Agati VD. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore). 2008;87(1):21-32. https://doi.org/10.1097/md.0b013e318161b0fc.
2. Pickering MC, D'Agati VD, Nester CM, Smith RJ, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013 Dec;84(6):1079-89. https://doi.org/10.1038/ki.2013.377.
3. Wada Y, Kamata M, Miyasaka R, Abe T, Kawamura S, Takeuchi K, Aoyama T, Oda T, Takeuchi Y. Clinico-Pathogenic Similarities and Differences between Infection-Related Glomerulonephritis and C3 Glomerulopathy. Int J Mol Sci. 2023 May 8;24(9):8432. https://doi.org/10.3390/ijms24098432.
4. Khalighi MA, Wang S, Henriksen KJ, Bock M, Keswani M, Meehan SM, et al. Revisiting post-infectious glomerulonephritis in the emerging era of C3 glomerulopathy. Clin Kidney J. 2016;9(3):397–402. https://doi.org/10.1093/ckj/sfw032.
5. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685–94. https://doi.org/10.1016/s1473-3099(05)70267-x.
6. Kambham N. Postinfectious glomerulonephritis. Adv Anat Pathol. 2012;19(5):338–47. https://doi.org/10.1097/pap.0b013e31826663d9.
7. Satoskar, A.A., Parikh, S.V. & Nadasdy, T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. Nat Rev Nephrol 16, 32–50 (2020). https://doi.org/10.1038/s41581-019-0178-8.
8. Marques Vde P, Neves PD, Mendonça HM, Fugikaha I, Fernandes EL. Acute glomerulonephritis after upper airway or skin infection: descriptive analysis of 82 cases between 14 and 64 years-old. J Bras Nefrol. 2010 Jul-Sep;32(3):237-41. PMID: 21103685.
9. Hamouda M, Mrabet I, Dhia NB, Aloui S, Letaif A, Frih MA, Skhiri H, Elmay M. Acute post-infectious glomerulonephritis in adults: a single center report. Saudi J Kidney Dis Transpl. 2014 May;25(3):567-71. https://doi.org/10.4103/1319-2442.132185.
10. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. In: Rovin BH, Adler SG, editors. KDIGO 2021. Kidney International; 2021. p. S172–86. https://doi.org/10.1016/j.kint.2021.05.021.
11. Sethi S, Nasr SH, De Vriese AS, Fervenza FC. C4d as a Diagnostic Tool in Proliferative GN. J Am Soc Nephrol. 2015 Nov;26(11):2852-9. https://doi.org/10.1681/ASN.2014040406.
12. Gupta N, Wakefield DN, Clapp WL, Garin EH. Use of C4d as a diagnostic tool to classify membranoproliferative glomerulonephritis. Nefrologia. 2017 Jan-Feb;37(1):78-86. https://doi.org/10.1016/j.nefro.2016.05.011.
13. Xu, F., Zhang, C., Zhang, M. et al. Evaluation of the significance of complement-related genes mutations in atypical postinfectious glomerulonephritis: a pilot study. Int Urol Nephrol 56, 1475–1485 (2024).