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Case Report

Internal Medicine Section

# Immune Complex-Mediated Crescentic Glomerulonephritis

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## ABSTRACT

Immune complex-mediated Glomerulonephritis (GN) comprises a group of disorders including Immunoglobulin A (IgA) nephropathy, IgA vasculitis, lupus nephritis, infection-related GN {poststreptococcal, Hepatitis C Virus (HCV)}, and fibrillary GN with polyclonal Immunoglobulin (Ig) deposits. Infection-Related Glomerulonephritis (IRGN) is an immune complex-mediated injury which is triggered by an infection other than renal causes. With new evolving histopathological variants such as C3 Glomerulonephritis (C3GN), it can be challenging to consultants in both diagnostic and management aspects in differentiating it from IRGN. It is seen to occur alongside infection in adults with a greater risk of disease progression to End-Stage Renal Disease (ESRD). Here, the authors report a case of 33-year-old male who presented with gastrointestinal and urinary symptoms. Patient was initially diagnosed as infective diarrhoea with Acute Kidney Injury (AKI), and on further evaluation, renal biopsy was suggestive of immune-complex mediated crescentic GN. Patient was treated with steroids and there was an improving trend of renal function and positive outcome after treatment, with an overall good prognosis. Aetiology of this immune-complex mediated crescentic GN is however, unclear due to similarities between Postinfectious Glomerulonephritis (PIGN) and C3 glomerulopathy pathologically.

**Keywords:** Acute nephritis, C3 glomerulopathy, Chronic kidney disease, Immunoglobulin, Infection-related

## CASE REPORT

A 33-year-old male with no known co-morbidities presented with chief complaint of fever since one week. Patient was apparently well one week prior to admission and later developed generalised fatigue followed by fever. Fever was insidious in onset, intermittent, low grade with evening rise of temperature and relieved with medication. Two days prior to admission, the fever was continuous, high grade, and was associated with chills and rigors. No history of night sweats, rash, sore throat, or weight loss.

He had a history of dark coloured urine, burning micturition, decreased urine output and decreased frequency for a week. There was no history of abdominal pain or flank pain. However, he reported with a history of facial puffiness, swelling of hands and feet for two days prior to admission. He had history of five episodes of loose stools one day prior to admission. Loose stools were watery in consistency, non blood tinged and non foul smelling. Patient also had one episode of vomiting on the day of admission. Vomitus contained food particles, it was non bilious and non blood tinged.

On presentation, patient was conscious and oriented. All vitals like temperature (97°F), pulse rate (87/min), Blood Pressure (BP) (140/80 mmHg), Saturation of Peripheral Oxygen ($SpO_2$) (98%) on room air and respiratory rate (18/minute) were within normal limits. General examination revealed facial puffiness with mild swelling of hands and feet. Swelling of the feet was confined to the medial malleolus and pitting in nature.

Systemic examination was normal. Routine investigations on the day of admission revealed elevated total counts (14,000 cells/$mm^3$) with normal haemoglobin and platelet count. Renal parameters were deranged {Urea: 46 mg/dL (Normal range: 15-45 mg/dL), Creatinine: 2.40 mg/dL (Normal range: 0.5-1.1 mg/dL)} and hypoalbuminemia (Albumin: 3 g/dL) was present. The urine routine showed albuminuria, 12-15 pus cells, 18-20 Red Blood Cells (RBCs) and granular casts. There was elevated urine protein creatinine ratio of 8.1 (Normal range: 0.1) and elevated 24 hour urinary protein excretion of 4.9 grams in 24 hours. Erythrocyte Sedimentation Rate (ESR) was elevated (90 mm/hour) and C-Reactive Protein (CRP) was negative. Fever profile for dengue, scrub, malaria and typhoid was negative. Lipid profile revealed hypertriglyceridemia (248 mg/dL). Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and HCV markers were negative. Ultrasonography of abdomen and pelvis showed normal sized kidneys and cortico-medullary differentiation was maintained. On admission, patient was provisionally diagnosed with probable infective diarrhoea and Acute Kidney Injury (AKI).

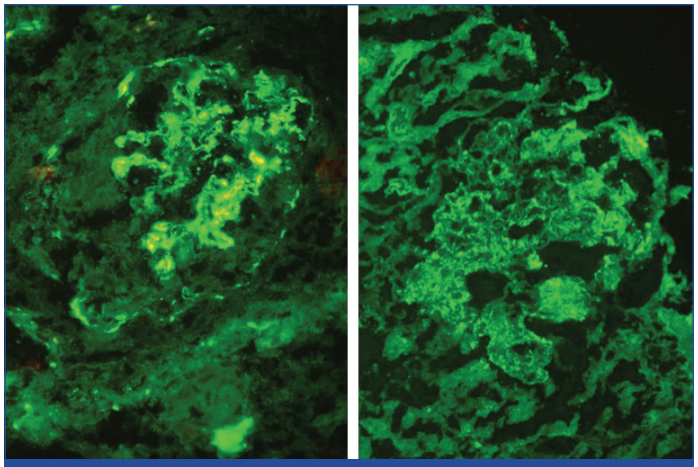
During the hospital stay, since day 2 of admission, the patient had persistent high blood pressure recordings (BP>170/100 mmHg) which were managed with calcium channel blockers (Oral nifedipine 20 mg 8$^{th}$ hourly). Due to elevated total counts and possible infective aetiology, patient was empirically treated with antibiotics and supportive medication such as intravenous fluids (0.9% normal saline). Due to a history of fever and dark coloured urine, statically elevated renal parameters and high blood pressure recordings in the hospital, our differential diagnosis included Acute Glomerulonephritis (AGN). Nephrology opinion was sought and they have advised for renal biopsy.

On day 4 of admission, BP continued to be elevated. Repeat renal parameters did not show any improvement (urea: 34 mg/dL and creatinine: 2.58 mg/dL). Total counts were on an improving trend. Blood and urine cultures were sterile. Renal biopsy was performed in strong suspicion of AGN. After the procedure, patient was monitored for haematoma and bleeding manifestations.

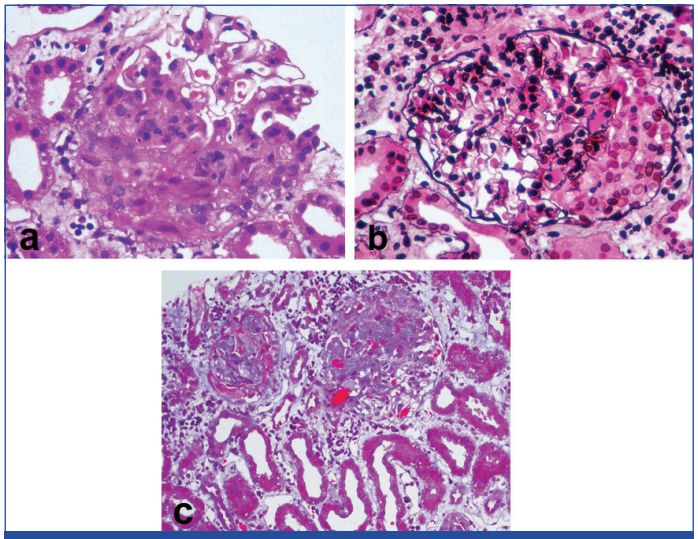
On day 6 of admission, renal biopsy findings were as follows: Immunofluorescence revealed granular positivity on the capillary loops and focally on the mesangium with C3 (+3) and IgG (+1) positive. No light chain restriction was seen. IgM, IgA and C1q were negative [Table/Fig-1,2].

Light microscopy with Haematoxylin and Eosin (H&E) stain, special stains like Periodic Acid-Schiff (PAS), Jones methenamine silver and Masson trichrome were done on the renal cortical tissue. Endocapillary hypercellularity was noted in all glomeruli. Cellular crescents were identified in five out of seven glomeruli. RBC casts were seen in many of the tubules with tubular epithelial cell injury and focal inflammatory infiltrate in the interstitium [Table/Fig-3].

With the renal biopsy findings suggestive of immune complex-mediated crescentic GN, the following autoimmune panel was done and the results were as shown in [Table/Fig-4].



**[Table/Fig-1]:** Granular positivity on capillary loops with C3 positive (enhanced).
**[Table/Fig-2]:** Granular positivity on capillary loops with IgG positive (enhanced). (Images from left to right)




**[Table/Fig-3]:** Light microscopy showing: a) Hypercellular and crescentic glomeruli; b) Red blood cell casts in tubules and c) Inflammatory infiltrate in the interstitium.

| Parameters | Result |
|---|---|
| **1. Autoimmune panel:** | |
| • C3 levels | Decreased (70.38 mg/dL; Normal: 90-180 mg/dL) |
| • C4 levels | Normal (25 mg/dL; Normal: 15-45 mg/dL) |
| • ANA | Negative |
| • p-ANCA and c-ANCA | Negative |
| **2. Anti-Streptolysin O titers** | Normal (<200 IU/mL) |

**[Table/Fig-4]:** Autoimmune panel with C3, C4 levels, ANA (Anti-Nuclear Antibodies), p-ANCA and c-ANCA (perinuclear- and cytoplasmic- Anti Neutrophil Cytoplasmic Antibodies), and Anti-Streptolysin O titers.

In view of the increasing trend of creatinine and with the above renal biopsy findings, the patient was also initiated on oral steroids-prednisone 30 mg/day.

On day 8 of admission, patient had no fever spikes or urinary symptoms, blood pressure was controlled with antihypertensives, urine output and renal parameters improved. Patient was discharged with steroids and antihypertensives and followed-up on outpatient basis. Investigations on follow-up are as mentioned in [Table/Fig-5].

On the first follow-up two weeks after discharge, the patient's renal parameters returned to baseline (urea: 34 mg/dL, creatinine: 1.16 mg/dL). Steroids were tapered (Oral prednisone 20 mg/day) and antihypertensives were continued. On further follow-up, repeat C3 levels at eight weeks after discharge were normal. Hence, steroids were further tapered and stopped.

| Investigations | Day 1: Admission | Day 4: Follow-up | Day 8: On discharge | 2 weeks: After discharge | 8 weeks: After discharge | Reference range |
|---|---|---|---|---|---|---|
| Total counts (cells/mm$^3$) | 14,000 | 11,500 | 7,700 | 10,000 | 9,000 | 4,000-11,000 |
| Urea (mg/dL) | 46 | 34 | 25 | 34 | 30 | 15-45 |
| Creatinine (mg/dL) | 2.40 | 2.58 | 1.79 | 1.16 | 1.10 | 0.5-1.1 |
| C3 levels (mg/dL) | 70.38 | - | - | - | 110 | 90-180 |

**[Table/Fig-5]:** Investigation chart on Day 1, 4 and 8 of admission, and on follow-up after discharge.

## DISCUSSION

Previously, a majority of IRGN cases occurred in children following a bacterial infection, most commonly streptococcal skin or upper respiratory tract infections, and were called Postinfectious Glomerulonephritis (PIGN). However, there has been a major paradigm shift in the epidemiology, aetiology, and outcomes of IRGN over the past few decades. A significant percentage of cases now target adults, particularly the elderly or immunocompromised [1].

Skin, oral mucosa/ teeth, cardiovascular, respiratory, and genitourinary tract are common sites of infection in adults. The time frame between the onset of renal disease and infection in children with PIGN is usually 1-4 weeks. But, in about half of the adult population, the infection is first detected at the onset of renal disease, indicating that infection may go unrecognised for a while [2]. A study showed that in 20% patients with endocarditis and 27% patients with pneumonia, the renal disease was diagnosed at the same time as infection [3]. In another study of six patients, among the five patients, the site of infection was urinary tract in two, urinary and respiratory tract in two and gastrointestinal tract in one, and all of them had concurrent infection at the time of development of acute nephritis [4]. However, this patient developed GN after acute febrile illness with both urinary and gastrointestinal symptoms.

The clinical differential diagnosis of IRGN in adults is broad and includes other glomerular diseases associated with a low complement level, such as cryoglobulinemic GN, Antineutrophil Cytoplasmic Antibody (ANCA)- associated pauci-immune GN, and C3 glomerulopathy. The presence of a low level of C3 with normal C4 favours IRGN or C3 glomerulopathy, and low C4 with normal C3 is more typical of cryoglobulinemic GN [2].

In IRGN, diffuse endocapillary proliferative and exudative changes with several intracapillary neutrophils are seen on renal light microscopy. Renal immunofluorescence in IRGN typically reveals C3-dominant or co-deposition of one or more immune reactants (IgG, IgM, IgA, C1q). IgG is usually the most frequent and intense immunoglobulin [2]. In a study of 86 patients, it was reported that diffuse endocapillary proliferative and exudative changes were seen in 72% patients, followed by focal endocapillary proliferation in 12% and mesangial proliferation in 8% patients. Formation of crescents is rare [5]. In this patient, renal light microscopy showed endocapillary hypercellularity in all glomeruli with cellular crescents in five out of seven glomeruli (71%). RBC casts were seen in many of the tubules with tubular epithelial cell injury and focal inflammatory infiltrate in the interstitium. Renal immunofluorescence showed granular mesangial and capillary wall staining for C3 (3+) and IgG (1+).

There is no single pathognomonic clinical or pathological finding for IRGN diagnosis in adults. Criteria to diagnose IRGN include atleast three of the following: (1) clinical or lab evidence of infection before or at the onset of GN; (2) low serum complement levels; (3) endocapillary proliferative GN; (4) hump-shaped subepithelial deposits on electron microscopy; and (5) C3-dominant or co-dominant immunofluorescence staining on glomeruli [2]. This patient satisfied 4 criteria for the diagnosis of IRGN. IRGN can be difficult to distinguish histologically from the C3GN which is associated with abnormalities in the alternative pathway of complement. The

glomerular positivity for C3 alone is unique for C3GN without staining for immunoglobulins or C1q. But, this can also occur in revolving phase of PIGN in one-fourth of patients [2,6]. In a study, IGRN biopsy samples were studied and they showed dominant C3 staining with weak to absent IgA and IgG [7]. Features favouring C3GN over IRGN in patients with sole C3 glomerular positivity are: persistently decreased C3 levels for more than several months, no clinical evidence of infection, active glomerulonephritis for several months, and large mesangial, subendothelial, and intramembranous deposits [2]. However, atypical cases can be triggered by infection, especially streptococcal as described in a study, and thus C3GN might masquerade as IRGN [8].

AKI has been rising in the past few decades. It is known to cause Chronic Kidney Disease (CKD), which may complicate to End-Stage Renal Disease (ESRD). Infection precipitating AGN is a major cause of AKI. In children, PIGN usually resolves without specific treatment, whereas prognosis of adult IRGN is poor. Older patients and immunocompromised patients, such as malignancies, diabetes mellitus, or alcoholism are reported to be at higher risk [9]. Therefore, in children, PIGN is considered as an acute condition that completely resolves without progression and with an overall favourable prognosis. This is in contrast to IRGN in adults, which most often than not, progress into chronicity with unfavourable renal prognosis [9]. A study revealed that 87% of adult patients with IRGN had renal insufficiency and 35.6% required dialysis, with 33.3% of patients progressing to CKD [10]. Genetic background of the host's complement system, persistent infection, tubulointerstitial changes, and pre-existing histological damage due to old age and co-morbidities are some factors that may contribute to the renal progression of IRGN [9,11].

In this patient, serum Antistreptolysin O (ASO) titres, ANA, cytoplasmic ANCA (c-ANCA), and perinuclear ANCA (p-ANCA) were negative, ruling out non infectious causes of immune-complex mediated crescentic GN. He had a low serum C3 level with a normal serum C4 level. He responded well to steroid therapy. Prednisone was tapered every week and stopped after one month of therapy from disease onset. In a study of PIGN with crescents in adults, it was observed that those patients who were treated with steroids had excellent response, but the duration of therapy was variable [4]. Similarly in the present case, the patient's renal parameters returned to baseline and repeat C3 levels were normal at 8 weeks, with an overall good prognosis. In C3GN, C3 levels tend to be constantly decreased even at 8-12 weeks of the onset of symptoms. Thus, indicating an infection-related cause of immune complex-mediated crescentic glomerulonephritis.

## CONCLUSION(S)

Authors reported this case to focus on the fact that aetiology of majority IRGN cases in young adults is unknown or might go unrecognised. Histopathological similarities between IRGN and C3GN can be confusing while arriving at a diagnosis. However, improvement of renal function and normal C3 levels after eight weeks of disease onset is likely to be IRGN, with an overall good prognosis in the present patient, considering many IRGN cases in adults progress to ESRD.

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