A STUDY OF CRESCENTIC GLOMERULONEPHRITIS – ETIOLOGY, CLINICAL PROFILE, PROGNOSTIC FACTORS AND OUTCOME

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CERTIFICATE

This is to certify that the dissertation entitled **"A Study of crescentic glomerulonephritis – etiology, clinical profile, prognostic factors and outcome"** is a bonafide work done by Dr.SP.S.SUBRAHMANIAN at the Nephrology department, Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of D.M., Degree in Nephrology (Branch III) under my guidance and supervision during the academic year 2007 – 2010.

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CONTENTS

BACKGROUND

Crescentic glomerulonephritis is the histologic manifestation of any severe glomerular injury resulting from immune/ inflammatory mechanisms. It is characterized by the proliferation of resident glomerular and infiltrating inflammatory cells in the Bowmans space. Rapidly Progressive Glomerulonephritis (RPGN) is the clinical counterpart of Crescentic glomerulonephritis and is characterized by a rapid decline in renal function over days to weeks. The urine sediment is typically active in RPGN, showing dysmorphic erythrocyturia and erythrocytic cylindruria.

RPGN is a medical emergency because of the potential for relentless and rapid progression to end stage renal failure, if not treated. The crescents evolve through various stages and ultimately transform into fibrous elements resulting in permanent glomerular scarring. Therefore therapeutic interventions in Crescentic glomerulonephritis should precede such irreversible alterations in glomerular structure. Early identification and treatment of RPGN gain importance in this respect.

Crescentic glomerulonephritis is the culmination of severe glomerular injury and the etiology of Crescentic glomerulonephritis is heterogeneous. The clinical presentation and immuno pathologic characteristics of Crescentic glomerulonephritis are influenced by the etiology. Identification of the etiology is essential for instituting appropriate treatment.

The annual incidence of Crescentic glomerulonephritis is 0.7 to 1.0 per 1,00,000 population[8]. Crescentic glomerulonephritis accounts for 9. 5% of glomerular diseases[4] and 5.1% of all biopsies done[5]. Geographic variations exist with respect to the incidence and etiology of Crescentic glomerulonephritis.

The present study has attempted to identify Crescentic glomerulonephritis and study the etiology, clinico epidemiological features and outcome of the disease in our region.

AIM OF THE STUDY

This study aims to identify patients with Crescentic glomerulonephritis and study the etiology, clinical profile, prognostic factors and outcome of Crescentic glomerulonephritis.

REVIEW OF LITERATURE

Rapidly progressive glomerulonephritis (RPGN) is defined as a rapid loss of renal function occurring over days to weeks (usually a 50% decline in the glomerular filtration rate within 3 months) in association with nephritic urine sediment. The histologic counterpart of RPGN is crescentic glomerulonephritis.

Glomerular crescents can complicate any glomerulopathy, and represent the phenotypic expression of severe glomerular inflammation.

Pathogenesis of crescentic glomerulonephritis:

Crescentic glomerulonephritis is the result of a final common pathway of glomerular injury that results in crescent formation. Multiple etiologies and pathogenic mechanisms can lead to the final common pathway, including many types of immune complex disease. The general dogma is that immune complex localization in glomerular capillary walls and mesangium, by either deposition or in situ formation or both, activates multiple inflammatory mediator systems. [46] This includes humoral mediator systems, such as the coagulation system, kinin system, and complement system, as well as phlogogenic cells, such as neutrophils, monocytes/macrophages, platelets, lymphocytes, endothelial cells, and mesangial cells. The activated cells also release soluble mediators, such as cytokines and chemokines. If the resultant inflammation is contained within the glomerular basement membrane, a proliferative or membranoproliferative phenotype of injury ensues with only endocapillary hypercellularity. However, if the inflammation breaks through capillary walls into Bowman space, extracapillary hypercellularity (crescent formation) results. Thus any severe glomerular injury producing breaks in the glomerular basement membrane can result in crescent formation.

Complement activation has often been considered a major mediator of injury in immune complex glomerulonephritis; however, experimental data indicate the importance of Fc receptors in immune complex mediated injury. [47, 48] For example, mice deficient for the Fc gamma R1 and Fc gamma R3 receptors have a markedly reduced capacity to develop immune complex glomerulonephritis.

Immunopathologic categorization of crescentic glomerulonephritis

Crescentic glomerulonephritis is categorized into three immunopathologic types based on the immunofluorescence characteristics.

- **Type I or Anti GBM disease**: Characterized by presence of linear deposits of immunoglobulin G along the glomerular basement membrane
- **Type II or** Immune **complex glomerulonephritis**: Characterized by the presence of granular deposits of immunoglobulin along the capillary wall or mesangium
- **Type III or Pauci immune nephritis**: Characterized by the lack of immune deposits in the glomerulus. This type of glomerulonephritis is considered as a manifestation of small vessel vasculitis. When Pauci immune nephritis occurs as an isolated manifestation, the condition is termed "renal limited vasculitis". Often the disease occurs as a renal manifestation of a more generalized systemic small vessel vasculitis.

Etiology of crescentic glomerulonephritis:

Crescents occur when breaks in glomerular capillaries allow leakage of cells and plasma proteins into Bowman's space. Crescents can therefore occur in almost any disease leading to glomerular inflammation, and sometimes in renal diseases that do not primarily affect the

glomerulus. Widespread crescent formation, however, requires active and specific attack on glomerular capillaries, and is found in a more restricted set of diseases. The etiopathogenesis of crescentic glomerulonephritis is summarized below

Type I or Anti GBM nephritis	Due to presence of circulating Anti GBM antibodies
Type II or Immune complex nephritis	Glomerular injury is mediated by in situ immune complex formation or by circulating immune complexes. Examples: 1) Post infectious glomeruli nephritis 2) IgA nephropathy 3) Membrano proliferative glomerulonephritis 4) Membranous nephropathy 5) Lupus nephritis 6) Henoch Schonlein nephritis 7) Cryoglobulinemia
Type III or Pauci immune nephritis	Systemic or renal limited small vessel vasculitis

Pathology

Light Microscopy

The light microscopic appearance of crescentic immune complex glomerulonephritis depends upon the underlying category of glomerulonephritis, for example, in their most aggressive expressions, membranoproliferative glomerulonephritis, membranous glomerulopathy, acute

postinfectious glomerulonephritis, or proliferative glomerulonephritis, including IgA nephropathy, can all have crescent formation. This underlying phenotype of immune complex glomerulonephritis is recognized best in the intact glomeruli or glomerular segments. There usually are varying combinations of capillary wall thickening and endocapillary hypercellularity in the intact glomeruli. This is in contrast to anti-GBM glomerulonephritis and ANCA-glomerulonephritis, which tend to have surprisingly little alteration in intact glomeruli and segments in spite of the severe necrotizing injury in involved glomeruli and segments. In glomerular segments adjacent to crescents in immune complex glomerulonephritis, there usually is some degree of necrosis with karyorrhexis; however, the necrosis rarely is as extensive as that typically seen with anti-GBM or ANCA-glomerulonephritis. In addition, there is less destruction of Bowman capsule associated with crescents in immune complex glomerulonephritis, as well as less pronounced periglomerular tubulointerstitial inflammation. Crescents in immune complex glomerulonephritis have a higher proportion of epithelial cells to macrophages than crescents in anti-GBM or ANCA glomerulonephritis, which may be related to the less severe disruption of Bowman capsule and thus less opportunity for macrophages to migrate in from the interstitium

Immunofluorescence Microscopy

Immunofluorescence microscopy, as well as electron microscopy, provides the evidence that crescentic glomerulonephritis is immune complex mediated versus anti-GBM antibody mediated versus likely to be ANCA-associated. The pattern and composition of immunoglobulin and complement staining depends on the underlying category of immune complex glomerulonephritis that has induced crescent formation. For example, crescentic glomerulonephritis with predominantly mesangial IgA-dominant deposits is indicative of

crescentic IgA nephropathy, C3-dominant deposits with peripheral band-like configurations suggest crescentic membranoproliferative glomerulonephritis, coarsely granular capillary wall deposits raise the possibility of crescentic post-infectious glomerulonephritis, and finely granular IgG-dominant capillary wall deposits suggest crescentic membranous glomerulopathy. The latter may be a result of concurrent anti-GBM disease, which will also cause linear GBM staining beneath the granular staining, or concurrent ANCA disease, which can be documented serologically. About a quarter of all patients with crescentic immune complex glomerulonephritis are ANCA-positive, whereas less than 5% of patients with non-crescentic immune complex glomerulonephritis are ANCA-positive. This suggests that the presence of ACA in patients with immune complex glomerulonephritis may predispose to disease that is more aggressive.

Electron Microscopy

As with the immunofluorescence microscopy, the findings by electron microscopy in patients with crescentic immune complex glomerulonephritis are dependent upon the type of immune complex disease that has induced crescent formation. The hallmark ultrastructural finding is immune complex-type electron dense deposits. These can be mesangial, subendothelial, intramembranous, subepithelial, or any combinations of these. The pattern and distribution of deposits may indicate a particular phenotype of primary crescentic immune complex glomerulonephritis, such as postinfectious, membranous, or membranoproliferative type I or II. Ultrastructural findings also may suggest that the disease is secondary to some unrecognized systemic process. For example, endothelial tubuloreticular inclusions suggest lupus nephritis, and microtubular configurations in immune deposits suggest cryoglobulinemia.

As with all types of crescentic glomerulonephritis, breaks in glomerular basement membranes usually can be identified if looked for carefully, especially in glomerular segments adjacent to crescents. Dense fibrin tactoids occur in thrombosed capillaries, in sites of fibrinoid necrosis, and in the interstices between the cells in crescents. In general, the extent of fibrin tactoid formation in areas of fibrinoid necrosis is less conspicuous in crescentic immune complex glomerulonephritis than in crescentic anti-GBM or ANCA glomerulonephritis.

Epidemiology:

The overall incidence of crescentic glomerulonephritis is between 2 and 5 per cent of unselected renal biopsies, regardless of the country of origin, be it France, England, America, India, or China (Whitworth *et al* . 1976 ; Neild *et al* . 1983 ; Woo *et al* . 1986 ; Date *et al* . 1987 ; Heilman *et al* . 1987 ; Parag *et al* . 1988 ; Tang *et al* . 2001 ; Vendemia *et al* . 2001). Men are affected twice as commonly as women, and Afro-Caribbeans are relatively rarely affected, except by crescentic SLE. In one study from South Africa, idiopathic crescentic glomerulonephritis and anti-GBM disease were more common in White than Black patients [(49)].

Clinical features:

Clearly, the precise clinical features of patients with crescentic glomerulonephritis vary with the underlying disease. Some features are relatively common to all causes of crescentic nephritis; hypertension is rare, loin pain not uncommon, constitutional symptoms found in approximately 50 per cent, urine almost always contains blood, red cell casts, granular casts, and protein, but nephrotic range proteinuria is rare. Rate of progression to renal failure is variable from hours (e.g. in anti-GBM disease) to months (some cases of MCGN).

Non-specific markers of inflammation are usually raised, including C-reactive protein (CRP), peripheral blood leucocytes, alkaline phosphatase, immunoglobulins and platelets, and serum albumin is usually depressed. There may be a normochromic normocytic anaemia. Specific investigations include ANCA [detected both by immunofluorescence and enzyme-linked immunosorbent assay (ELISA)] and anti-GBM antibodies, and markers for SLE [ANA, anti-double-stranded DNA (dsDNA) antibodies, serum complement]. These are the crucial investigations in all patients with RPGN. Imaging is usually non-specifically abnormal. Ultrasound will show swollen, echogenic kidneys with loss of the corticomedullary junction.

Prognostic factors:

Objective assessment of the response to treatment of crescentic glomerulonephritis has been confounded by the heterogeneity of diseases included in most studies. It has become very clear over the last decade that the underlying immunopathological drive to crescent formation makes a substantial contribution to the outcome, but more importantly other biopsy features predict outcome much more than crescents themselves [(26)]. As with other primary glomerulonephritides, the extent of tubulointerstitial scarring is a better marker of poor prognosis than a crescent score in almost all diseases causing crescentic glomerulonephritis. In anti-GBM disease, high crescent scores are associated with a worse outcome, but interstitial scarring better predicts lack of reversibility. In ANCA-associated vasculitis, the number of normal glomeruli and not the number of crescents is associated with renal recovery, and in IgA disease most studies have not demonstrated a worse outcome in patients with crescents in glomeruli. Renal function at presentation independent of histology is also a powerful predictor of outcome, and in clinical trials patients should be stratified by renal function as well as by precise diagnosis [(27)].

Treatment of crescentic glomerulonephritis:

In general, treatment is often divided into two phases in crescentic glomerulonephritis. First is induction of remission during the acute phase, followed by the next phase of maintenance therapy to control the underlying immunopathology in the longer term. The induction phase of treatment should both suppress the acute inflammatory features of crescentic glomerulonephritis and control the underlying aberrant immune response, while the maintenance phase should prevent scarring and prevent recrudescence of acute inflammation. Thus, in anti-GBM disease, plasma exchange removes circulating pathogenic autoantibodies, while prednisolone and Cyclophosphamide (and possibly other effects of plasma exchange) suppress the acute inflammatory response, cell infiltration, and further antibody synthesis. Prior to the use of any immunosuppressive therapies, the mortality from crescentic glomerulonephritis was 100 percent [(28)]. Steroids improved the survival but only 25 per cent of patients escaped the need for dialysis. Patients with crescentic glomerulonephritis due to poststreptococcal glomerulonephritis had a better outcome. More recently, the prognosis for renal recovery has improved with the earlier diagnosis of crescentic glomerulonephritis, more precise disease characterization, and more carefully targeted treatments[(29)], although some studies fail to demonstrate any improvement in renal or patient survival over the last two decades[(2)] . The mainstay of therapy has remained relatively non-specific immunosuppression with combination therapies including steroids, Cyclophosphamide and Azathioprine, with or without methylprednisolone and plasma exchange.

Plasma exchange in crescentic nephritis

Plasma exchange has been used to treat almost all causes of crescentic glomerulonephritis, but with little controlled data in most instances. In anti-GBM disease, the rationale is clearly to remove pathogenic autoantibodies, but the process also has effects on inflammatory mediators and possibly cell-mediated immune function. Prior to the introduction of plasma exchange, almost all patients died and renal recovery was rare [30]. The largest experience of plasma exchange was reported by Levy et al.,[31] in 71 patients treated intensively with plasma exchange, prednisolone and cyclophosphamide, with excellent renal and patient survival in patients presenting with mild or moderate renal failure. Patients presenting with dialysis-dependent renal failure rarely, but occasionally, recovered renal function. Other groups have used less intensive regimens, which may well affect the potential benefit of therapy.

The benefits of plasma exchange in anti-GBM disease subsequently led to the more widespread use of the treatment in other crescentic glomerulonephritides, especially in pauci-immune vasculitis (Rifle *et al* [32] ; Muller *et al* [33]). The identification of the pathogenic role of ANCA antibodies has strengthened the rationale for plasma exchange in this setting. There have been a number of controlled trials reported since 1988, and the most cohesive study was reported by Pusey *et al* [34] in which only patients with non-anti-GBM pauci-immune crescentic nephritis were enrolled into a prospective, randomized trial. Plasma exchange was of significant benefit to patients presenting with severe renal failure requiring dialysis, but not to those with lesser degrees of renal impairment. The overall consensus from all these studies was that plasma exchange may offer benefit to patients with severe renal failure, but not to those with creatinine less than 500 μmol/l [35]. This data prompted the multi-centre prospective randomized controlled

MEPEX trial, in which 151 patients with ANCA-associated crescentic glomerulonephritis and creatinine greater than 500μmol/l were randomized to plasma exchange or intravenous methylprednisolone as induction treatment in addition to conventional oral immunosuppression. The results clearly showed the benefit of plasma exchange in this group of patients with severe renal failure, with around 70 per cent coming off dialysis when treated with plasma exchange, but only 50 per cent recovering renal function when treated with methylprednisolone. Evidence for the benefit of plasma exchange in all other crescentic nephritides is poor [35]. A controlled trial of plasma exchange (performed relatively infrequently) in SLE with moderate renal dysfunction has shown no benefit. One small series of patients with crescentic IgA disease has been reported in whom plasma exchange may have improved outcome [36].

Methylprednisolone in crescentic nephritis

Intravenous methylprednisolone has been used extensively in all forms of crescentic nephritis [35, 37, 38]. Only controlled comparison is the MEPEX study comparing plasma exchange with methylprednisolone in ANCA-associated crescentic glomerulonephritis with severe renal failure in which methylprednisolone was significantly worse at improving renal function. There have been no controlled comparisons of oral versus intravenous steroids, and there is a suggestion that intravenous steroids may be associated with an increased risk of osteoporosis, avascular necrosis and infection. Roccatello *et al* [39] have reported 12 patients with crescentic IgA disease treated with intravenous methylprednisolone followed by oral immunosuppression, in whom the 5-year renal survival was significantly improved compared to an untreated group (91.6 per cent versus 37.5 per cent). This was not, however, a randomized prospective controlled study.

Other induction treatments

All treatment regimens for crescentic glomerulonephritis now include cyclophosphamide, since the demonstration of greater efficacy than azathioprine in patients with Wegener's granulomatosis[40] and microscopic polyangiitis,[41] but there is continued debate as to the benefit of oral versus intravenous treatment. A number of trials have been performed with ambiguous results, and in general, it seems that toxicity and side-effects are less with an intravenous regimen, but that efficacy in controlling renal inflammation is also reduced. De Groot's meta-analysis of the rather sparse data (143 patients enrolled into a number of studies) showed that pulse cyclophosphamide was significantly less likely to fail to induce remission (OR 0.29; 95% CI 0.12–0.73) and had a significantly lower risk of infection and leucopenia, but relapses occurred slightly (but not statistically significantly) more often. Intravenous immunoglobulin (at 2 g/kg over 3–5 days) has been used in a number of studies and appears to be beneficial in the short term, but with a risk of an acute deterioration in renal function[42]. Treatment with chlorambucil, cyclosporin, mycophenolate, and anti-lymphocyte globulin has also been reported anecdotally in a few patents with crescentic glomerulonephritis. Anti-TNF therapy with either blocking antibodies (infliximab) or soluble receptors (eternacept) may be of benefit in ANCA-associated diseases.

Maintenance therapy

The need for maintenance therapy in crescentic glomerulonephritis depends on the underlying disease. Long-term maintenance therapy is needed in almost all patients with ANCA-associated disease, since 50 per cent will relapse either with local or systemic disease, and long-term treatment can reduce relapses significantly[43]. The CYCAZAREM trial clarified the optimum

therapeutic regimen by demonstrating that oral azathioprine after induction of remission was as effective as oral cyclophosphamide with a trend to less short-term toxicity, and undoubted longer-term benefits[44]. Few, if any, patients with ANCA-associated crescentic glomerulonephritis should now remain on cyclophosphamide beyond 3 months. Patients relapsing on azathioprine may require further cyclophosphamide. Alternative agents include mycophenolate, anti-TNF therapy, cyclosporin, leflunomide, deoxyspergualin, and methotrexate (if renal function preserved). In contrast, anti-GBM disease is not a relapsing disease, and patients do not require long-term maintenance therapy. Patients can stop cyclophosphamide at 3 months and be 'weaned' off steroids by approximately 6 months. There are no good data on the length of immunosuppression needed in patients with primary glomerulonephritis in crescentic phase, but where treatment has been initiated, it would be necessary to continue low-dose maintenance immunosuppression (prednisolone and azathioprine) for 1–2 years. In addition to ongoing immune-mediated damage, patients are also at risk of progressive renal decline from haemodynamic factors and progressive scarring, independent of the initial insult. This seems more likely in all crescentic glomerulonephritides if patients make only a partial recovery after induction treatment, and if their serum creatinine does not reduce to less than 250 μmol/l. Distinguishing relapse from progressive scarring can be very difficult, but is clearly an important distinction. Rebiopsy will help, and monitoring circulating ANCA may also be useful, although there are few studies to support the use of serial ANCA alone in guiding decisions about immunosuppression[45].

MATERIALS AND METHODS

Patients presenting to the Department of Nephrology, Madras Medical College with the clinical syndrome of Rapidly Progressive Glomerulonephritis (RPGN) from January 2008 to March 2010 were identified and subjected to physical examination, a range of non invasive investigations and renal biopsy to establish the presence of crescentic glomerulonephritis. Those individuals in whom the renal biopsy revealed crescentic glomerulonephritis were included in the study and analyzed for the etiology, clinical profile, prognostic factors and outcome.

Inclusion criteria:

1) Patients with crescentic glomerulonephritis in renal histopathology were included in the study. Crescentic glomerulonephritis was defined as involvement of atleast 50% of the total number of glomeruli in renal biopsy (in other words "diffuse" crescents).
2) Both sexes and individuals more than 12 years of age were included.
3) Individuals with preexisting co morbidities – hypertension, previous cerebro vascular accident, chronic liver disease to mention a few, were also included.
4) Patients with pre existing glomerular diseases like IgA nephropathy, Henoch Schonlein Purpura and diffuse proliferative Lupus nephritis were included in the study if they presented with RPGN and renal biopsy revealed crescentic glomerulonephritis.
5) Pregnant patients presenting with crescentic glomerulonephritis were also included.

Exclusion criteria:

1) Renal biopsy samples with focal crescent formation, defined as involvement of less than 50% of the total number of glomeruli, were labeled as "glomerulonephritis with crescents" and were not included for further analysis.

2) Children who were 12 years or younger.

Cinical evaluation:

Historic evaluation was focused on identifying the major renal manifestations of RPGN like oliguria, anuria, haematuria and edema, extra renal symptoms like arthralgia, skin rash, haemoptysis etc., and the duration of presenting symptoms. Precipitating events like respiratory infection, skin infection, drugs, smoking, and exposure to toxins or non adherence to prescribed medications in patients with preexisting diseases like Lupus nephritis were looked for. Co morbid diseases were identified. Thorough clinical examination, including general assessment, BP measurement, fundus examination, ENT examination and systemic examination was performed in all patients.

Investigations:

Urine analysis, complete haemogram, coagulation profile, renal function tests and liver function tests were performed at entry and were repeated as necessary. Chest X-ray and ultrasonogram of KUB (Kidney, Ureter and Bladder) were routinely performed. CT scan of chest and paranasal sinuses were performed in selected patients (in suspected vasculitis and Anti GBM disease or in those with symptoms related to chest or sinuses). Investigations necessary for evaluation of co morbidities like MRI and CT scan of brain for evaluation of weakness of limbs, upper gastro intestinal endoscopy for decompensated liver disease etc., were carried out. Serologic testing for Hepatitis B and C viruses and Human Immuno deficiency virus were done in all patients.

Serologic work up for RPGN included assessment of serum complement profile (C3 and C4), ANA (Anti Nuclear Antibody) testing, ASO (Anti Streptolysin O) titer, P and C – ANCA

(Anti Neutrophil Cytoplasmic Antiboby) testing and Anti GBM antibody testing. In any patient serologic evaluation proceeded in a systematic manner as described in the review of literature. The method of ANA testing varied between patients. In some, it was performed by immunofluorescence while in others ELISA(Enzyme Linked Immuno Sorbent Assay) was employed. A titer of 1/100 or more in ELISA was taken as positive. Anti double stranded DNA was tested in those who were ANA positive. ANCA testing was done by immunofluorescence analysis of ethanol fixed neutrophils. ASO level more than 200 units/ml was considered significant. Anti GBM antibody testing was done by ELISA employing engineered glomerular basement membrane.

Renal biopsy was performed in all patients with RPGN after ultrasonographic localisation. Light microscopic analysis after staining with Haematoxylin and Eosin, Periodic Acid Schiff and Silver methanamine and immunofluorescence microscopy was done in all samples. Interpretation of results was done by a trained nephro pathologist.

Based on the immunofluorescence picture, Crescentic glomerulonephritis was categorized into three types, namely Anti GBM nephritis, Immune complex nephritis and Pauci immune nephritis as detailed in the review of literature.

Establishing the etiology and therapeutic interventions:

The etiology of Crescentic glomerulonephritis was established by considering the immunofluorescence pattern in renal biopsy and the results of serologic investigations as summarized in the review of literature. Standard treatment protocols recommended in literature for each specific etiology of Crescentic glomerulonephritis (ex. Crescentic Lupus nephritis,

Crescentic IgA nephropathy, Anti GBM nephritis, Vasculitis etc.,) and reviewed in the previous section were adapted.

Measures of outcome: [9]

Patients were followed up for a maximum of six months. The renal function, proteinuria and status of extra renal complications were periodically assessed during these six months of follow up. The findings at specified time points (one, three and six months) were recorded as follows.

1) Status – alive or dead
2) Extent of recovery of renal function – complete recovery (if renal function touched base line) partial recovery (patient became dialysis independent, but renal function had not touched baseline value) or no recovery (patient dialysis dependent)
3) Remission of proteinuria - complete remission(trace or less than trace proteinuria), partial remission (reduction in proteinuria by atleast 50% from the base line), no remission (not even partial remission achieved).

Outcome at three months was regarded as "favorable" if there was complete or partial recovery of renal function and as "adverse" if patient remained dialysis dependent or died.

Assessment of prognostic factors:[9]

The following factors were analyzed for prognostic significance.

1) Age
2) Urine output at presentation

3) Requirement for dialysis

4) Blood Pressure at presentation

5) Time duration between symptom onset & initiation of specific treatment

6) Histological parameters like extent of crescent formation, necrotizing lesions, chronic changes involving the glomeruli and tubulo interstitium

7) Etiology of crescentic glomerulonephritis

Patients were categorized in to two groups based on the outcome – "Responders" had favorable outcomes and "non responders" had adverse outcomes. The various clinical and histologic parameters were compared between the two groups for assessing their prognostic significance.

Statistical analysis:

Comparisons of clinical and histologic data between subgroups were performed using Student's *t*-test for unpaired data, as well as the one-way ANOVA (Analysis of Variance). Relationships between parametrical parameters were determined using Pearson's correlation coefficient.

Statistical analysis was performed using a computer program package (SPSS 10.1 for Windows, Standard version, ©SPSS.Inc.), and a P value of < 0.05 was considered significant.

RESULTS

Patients presenting to the Nephrology department with the clinical syndrome of RPGN (Rapidly Progressive Glomerulonephritis) from Jan 2008 to March 2010 were identified and investigated as per the protocol mentioned.

A total of 79 patients with RPGN were identified. Renal histopathology revealed diffuse crescentic glomerulonephritis in 26 patients. In the remaining 53 patients, renal biopsy revealed focal crescent formation in 41 patients and only diffuses endocapillary proliferation in 12 patients.

The 26 patients with Crescentic Glomerulonephritis were included in the study and analyzed for the clinical presentation, etiology, outcome and prognostic factors.

The study population included 11 males & 15 females. The mean age of the population was 32.96 years and the age ranged from 14 years to 70 years.

In most patients crescentic glomerulonephritis occurred as a denovo manifestation i.e., in patients in whom there was no histological or clinical evidence of preexisting glomerulonephritis. A few patients had preexisting glomerulonephritis - five patients were known to have proliferative lupus nephritis and one patient had Henoch Schonlein purpura.

Several comorbid illness were noted in the study population which included DCLD (decompensated liver disease) with portal hypertension and esophageal varices in one patient, previous arterial hypertension and cerebrovascular accident with residual weakness in another, lymphedema of lowerlimbs due to filariasis in another and an incidentally detected Hepatitis B

virus infection(non replicative infection without transaminitis) in one patient. In two patients crescentic glomerulonephritis manifested during the last trimester of pregnancy.

In eleven patients, fever preceded or occurred along with RPGN. Three of them also had diarrheal episodes. Two patients had symptoms of respiratory tract infection prior to the clinical presentation as RPGN. One patient had an unknown insect bite over lower limb, with a nodular eruption, one week prior to onset of symptoms. Three patients admitted taking drugs (for fever, diarrhea) prior to onset of edema & oliguria but the exact medications could not be identified. In one patient scabies antedated RPGN. In twelve patients no such apparent provoking events could be identified (Fig.1).

The major symptoms at presentation included edema, oliguria, anuria and haematuria occurring to variable degrees (Fig.2). While edema was a universal occurrence, urine output varied considerably among patients with crescentic glomerulonephritis. Nine patients had oliguria (defined as urine output <500 ml/24 hours), eight patients had anuria(defined as urine output < 100 ml/24 hours) and the remaining nine patients remained nonoliguric (Fig.3). Visible haematuria occurred in seven patients.

Various extra renal manifestations found are depicted in Fig. 4. Arthralgia was the predominant extra renal manifestation, observed in eight patients, one of whom had preexisting Henoch Schonlein purpura and the remainder had preexisting diffuse proliferative lupus nephritis.

Three patients had skin rash. Palpable purpura and erythema nodosum were the pertinent skin findings observed. One patient had fixed drug eruption.

Haemoptysis was the presenting feature in a 15 years male and a CT scan of chest done later revealed diffuse air space consolidation bilaterally. Pleurisy accompanied RPGN in one patient. Three patients developed generalized seizures and weakness of limbs occurred in two patients. Weakness was accounted by spinal and frontal demyelination in MR imaging in one patient and the other had evidence of infarct in the territory of the MCA (Middle Cerebral Artery). One of the two pregnant patients developed antepartum haemorrhage at eighth month of gestation.

Hypertension (defined as a BP ≥ 140/90 mm Hg) was detected at presentation in twenty five patients. Four were initiated on antihypertensive medications in other centers before their referral to Nephrology department. One patient was normotensive (BP 120/80 mm Hg) at the time of presentation. 42.3% had BP ≥ 161/101 mm Hg and 38.5% had BP between 141/91 and 160/100. The average BP of the population was 166.18/100 mm Hg. Hypertensive neuroretinopathy was recognized in six patients. Findings are summarized in BOX 1 and Fig.5.

Box 1: BLOOD PRESSURE AT PRESENTATION IN CRESCENTIC GLOMERULONEPHRITIS

Number of patients already instituted anti - hypertensive drugs	Number of patients (as % of total) with BP < 140/90 mm Hg	Number of patients(as % of total) with BP 141/91 to 160/100 mm Hg	Number of patients (as % of total) with BP ≥161/101 mm Hg
04 (15.4%)	01 (3.8%)	10 (38.5%)	11 (42.3%)

In all the twenty six patients with crescentic glomerulonephritis, immunofluorescence analysis of renal biopsy specimen was done which enabled categorization of crescentic glomerulonephritis into three types (Fig.6). Immune complex glomerulonephritis was found to be the most common cause of Crescentic Glomerulonephritis accounting for 69.2% of all cases. Pauci immune Crescentic Glomerulonephritis (vasculitis) contributed to 23.0% of all cases. Anti GBM nephritis was the least common variety accounting for 7.8% of crescentic glomerulonephritis.

Further identification of the etiology in immune complex glomerulonephritis was based on the immunofluorescence findings and serological investigations as detailed previously. A half of immune complex crescentic glomerulonephritis was due to lupus nephritis. Post Infectious Glomerulonephritis and IgA nephropathy each constituted 22.2% and membranous nephropathy 5.6% of immune complex crescentic glomerulonephritis (Fig.7)

The clinical characteristics of each immunopathologic type of crescentic glomerulonephritis are summarized below. The urine out put at presentation in each type is shown in Fig.8. Both the patients with anti GBM nephritis presented with anuria, while the urine output varied considerably among patients with immune complex glomerulonephritis and pauci immune nephritis.

The average blood pressure at presentation in each category is shown in Box 2. Hypertension was found to be most pronounced in immune complex nephritis.

Box 2: BP AT PRESENTATION IN CRESCENTIC GLOMERULONEPHRITIS

Category of Crescentic Glomerulonephritis	Average BP in mm Hg
Anti GBM nephritis	163.0/105.0
Immune Complex nephritis	170.6/99.6
Pauci immune nephritis	152.6/91.6

Extra renal manifestations varied according to the etiology of crescentic glomerulonephritis and are summarized in Box 3. Out of the two patients with Anti GBM nephritis one had evidence of pulmonary haemorrhage. The clinical presentation of crescentic lupus nephritis was characterized by coexpression of a plethora of extra renal manifestations like arthralgia, pleurisy, skin rash, oral ulcers and CNS manifestations. One of the two patients with Henoch-Schonlein nephritis manifested palpable purpura along with crescentic glomerulonephritis. Spinal and frontal demyelination occurred along with PIGN. No extra renal manifestations were observed in patients with vasculitis, implying that vasculitis was mainly renal limited in this series.

Box 3: PROFILE OF EXTRA RENAL MANIFESTATIONS IN CRESCENTIC GLOMERULONEPHRITIS

Etiology of Crescentic Glomerulonephritis	Extra renal manifestations
Anti GBM nephritis	Pulmonary haemorrhage
Lupus nephritis	Arthralgia, Erythema Nodosum, oral ulcers, seizures CVA (Middle Cerebral Artery territory infarct), pleurisy
Henoch Schonlein purpura	Palpable purpura, arthralgia
Vasculitis	None
IgA nephropathy	Antepartum haemorrhage
PIGN	Demyelination of spine and frontal region

The average urinary protein excretion at presentation in each category of crescentic glomerulonephritis is shown in Fig.9. The highest mean spot urine protein creatinine ratio was seen in Anti GBM nephritis (6.30) followed by immune complex glomerulonephritis (5.92) and pauci immune nephritis (3.46)

The results of serologic investigations varied according to the etiology of crescentic glomerulonephritis. The findings in each category are summarized below (Box 4 through 8).

BOX 4: SEROLOGIC PROFILE OF ANTI GBM NEPHRITIS

Total number of patients	2
Number of patients positive for Anti GBM antibody	2
Serum complement(C3 & C4)	Normal in all patients
ANA	Negative in all patients
Number of patients tested for ANCA (p & c)	1
Number of patients positive for p ANCA	1
Number of patients positive for c ANCA	0

BOX 5: SEROLOGIC PROFILE OF CRESCENTIC LUPUS NEPHRITIS

Total number of patients	9
Serum C3	Low in all patients
Serum C4	Low in all patients
ANA	Positive in 5 patients, negative in 2 patients
Anti ds DNA	Positive in 5 patients, negative in 1 patient

BOX 6: SEROLOGIC PROFILE OF CRESCENTIC POST INFECTIOUS GLOMERULONEPHRITIS

Total number of patients	**4**
Serum C3	Low in all patients
Serum C4	Normal in all patients
ASO	Positive in 1 patient, negative in 1 patient
ANA	Positive in 1 patient, negative in 2 patients

BOX 7: SEROLOGIC PROFILE OF CRESCENTIC IGA NEPHROPATHY & HENOCH SCHONLEIN NEPHRITIS

Total number of patients	4
Serum C3 & C4	Normal
ANA	Negative

BOX 8: SEROLOGIC PROFILE OF VASCULITIS

Total number of patients	6
Serum C3 & C4	Normal in all patients
P - ANCA	Positive in 2 patients, negative in 4 patients
C - ANCA	Negative in all patients
ANA	Negative in all patients

Both patients with Anti GBM nephritis by histology demonstrated circulating Anti GBM antibodies. Out of the nine patients who had immunofluorescence feature and complement profile suggestive of lupus nephritis (both C3 and C4 low), ANA(anti nuclear antibody) was tested in seven patients and found to be positive in five patients and negative in the remaining two(Fig.10). Anti double stranded DNA (Anti ds DNA) was tested in six patients and found to be positive in five patients.

ASO(anti streptolysin O) titer was determined in two out of four patients with PIGN and was found to be high in one patient. One patient with complement profile and histology suggestive of PIGN tested positive for ANA.

ANCA (Anti neutrophil cytoplasmic antibody) testing was done in all six patients with pauci immune nephritis. P-ANCA was found to be positive in two out of six patients with pauci immune nephritis and negative in the remainder. C-ANCA was not detectable in any of these patients. Thus the majority of patients with vasculitis lacked any detectable circulating ANCA (Fig 11).

All patients with IgA Nephropathy by histopathology demonstrated normal serum complements and were negative for ANA.

Renal biopsy was performed in all 79 patients with RPGN. Three patients had transient visible haematuria following biopsy. No other complications related to renal biopsy was encountered. Only those patients with the histologic feature of circumferential crescent formation in atleast 50% of the glomeruli were included in the study. The extent of crescent formation in the study population ranged from 50% to 100%. On an average 77.46% of the glomeruli in the study samples revealed crescent formation. All ages of crescents were noted. Cellular crescents alone were seen in thirteen patients, fibrocellular crescents alone in six patients, fibrous crescents alone in two patients and a combination of cellular and fibrocellular crescents in five patients(Fig.12). Glomerular tuft necrosis was seen in three patients, two of whom had Anti GBM nephritis and the other patient had pauci immune nephritis (p–ANCA positive). The same patient with pauci immune nephritis showed intracapillary fibrin deposition along with glomerular tuft necrosis. Glomeruli or segments of glomeruli not involved in crescent formation were studied for endocapillary proliferation. Diffuse glomerular proliferation with or without exudation was seen in thirteen patients. Capillary wall thickening was evident in eight patients. To enable clinicopathologic correlation chronic tubulo interstitial changes were graded as none, mild, moderate and severe. Accordingly mild, moderate, severe and no chronic tubulo interstitial

changes were seen in twelve, four, two and eight patients respectively (Fig.13). Blood vessels appeared normal or thickened. Fibrinoid necrosis of an arteriole was observed in one patient who had pauci immune nephritis.

Average serum creatinine at presentation was 642µmol/L (range: 130 to 2413 µmol/L). Twenty three out of twenty six patients required dialysis during the course of follow up. All the twenty five patients with hypertension required oral antihypertensive drugs. Specific therapeutic measures included administration of immunosuppressive drugs like corticosteroids (IV pulse, oral), cyclophosphamide, Mycophenolate mofetil and institution of plasmapheresis. The decision to use a particular immunosuppressive regimen in each patient was based on the etiology of crescentic glomerulonephritis and the clinical and histologic characteristics as already addressed in the literature review. Twenty patients were managed with immunosuppressive measures. Two of them also required plasmapheresis (one patient with anti GBM nephritis and pulmonary haemorrhage and the other with vasculitis and severe renal failure). Six patients did not receive any form of immunosuppression. Late presentation with advanced sclerosing lesions in histopathology or comorbidities like liver disease, portal hypertension and esophageal varices and pyelonephritis precluded immunosuppression in these patients. Fig.14 depicts the extent of usage of immunosuppressive drugs and other strategies in the study population. The occurrence of crescentic glomerulonephritis in the third trimester of two pregnant patients warranted termination of pregnancy.

Adverse reactions related to immunosuppressive therapy included gastro intestinal side effects like nausea, vomiting and dyspepsia. One patient with Crescentic Lupus nephritis developed febrile neutropenia following fourth (monthly) pulse of Cyclophosphamide and expired because of sepsis. In others Cyclophosphamide appeared to be well tolerated without any

serious adverse effects like haemorrhagic cystitis or bone marrow suppression during the study period.

The mean delay between the occurrence of first renal symptom of crescentic glomerulonephritis and the institution of specific therapy was 17.45 days. This was accounted for by a mean delay of 13.76 days between onset of first renal symptom and presentation to clinic.

Patients were followed up at regular intervals upto a maximum of six months. A minimum of a month's follow up was available for all patients. The mortality rate during the follow up period was 15.38%, i.e., four out of twenty six patients died, with two deaths occurring within three months of diagnosis and the remainder two occurring within six months. Death occurred due to noncompliance with dialysis and pulmonary edema in one patient, neutropenia and sepsis (secondary to immunosuppression) in one patient and psoas abscess and sepsis (not given immunosuppression) in another patient. One patient with anti GBM nephritis died of pulmonary haemorrhage.

At three months nineteen patients continued to follow up, five patients had defaulted and two expired. Out of these nineteen patients, seven patients remained dialysis dependent, nine patients became dialysis free and three patients never required dialysis (Fig.15). In those who became dialysis free the average duration of dialysis dependency was 32.5 days. Renal function approached base line with serum creatinine falling less than 132 μmol/l (1.5 mg/dl) in four patients. The other five patients who became dialysis independent had a partial recovery of renal function with an average serum creatinine of 248 μmol/l. Out of the five patients who had defaulted at three months, three remained dialysis dependent and two became dialysis independent by one month.

At six months thirteen patients lost follow up, three patients died, four patients remained dialysis dependent, six patients were dialysis free. The status of patients at various time periods is shown in Fig.16. The outcome according to the immunopathologic categories is summarized in Box 9.

Box 9: OUTCOME AT 3 MONTHS ACCORDING TO IMMUNOPATHOLOGIC CATEGORIES

Category	Anti GBM nephritis (n=2)	Immune complex nephritis (n = 18)	Pauci immune nephritis (n = 6)
ESRD	1 (50%)	6 (33.33%)	0
Partial recovery of renal function	0	4 (22.22%)	4 (66.66%)
Serum creatinine < 1.5 mg%(132 µmol/L)	0	4 (22.22%)	0
Death	1 (50%)	1 (5.55%)	0
Lost follow up	0	3 (16.66%)	2 (33.33%)

Figures inside the box represent number of patients (as % of number of patients in each category)

The outcome at three months was considered "favorable" if there was partial or complete recovery of renal function and "adverse" if there was no recovery of renal function, i.e., patient developed ESRD (End Stage Renal Disease) or if the patient died. Accordingly those who had a favorable outcome were categorized as "Responders" and those whose outcome was adverse were categorized as "Non responders" (Box 10).

BOX 10: PATIENT CATEGORIZATION ACCORDING TO OUTCOME AT THREE MONTHS

Category	Responders	Non responders
Anti GBM nephritis (n = 2)	0	2
Immune complex nephritis (n=18)	8	7
Pauci immune nephritis (n=6)	4	0

The rate of complete and partial remission of proteinuria at three and six months for the three different immunopathologic categories of Crescentic Glomerulonephritis is shown in Box 11.

BOX 11: STATUS OF PROTEINURIA AT 3 MONTHS IN CRESCENTIC GLOMERULONEPHRITIS

Category	3 months	
	Partial remission	Complete remission
Anti GBM nephritis (n = 2)	0%	0%
Immune complex nephritis (n = 18)	6 (33.33%)	0%
Pauci immune nephritis (n = 6)	4 (66.66%)	0%

The clinical and histologic parameters were compared between two groups (responders and non responders) and are summarized in Box 12. Among the several factors that were assessed for prognostic significance, the average crescent score showed the maximum significance with a P value of 0.01. The percentage of glomeruli with fibrous or fibrocellular crescents also differed significantly between the two groups (P = 0.02). In responders only 26.45% of the glomeruli revealed fibrous/fibrocellular crescents while in non responders 69.54%

of the sampled glomeruli demonstrated fibrous/fibrocellular crescents. The average diastolic BP between the two groups varied significantly. Other parameters like age, urinary protein excretion, mean latency to specific treatment, systolic BP and the requirement for dialysis failed to show a prognostic value.

BOX: 12: ASSESSMENT OF PROGNOSTIC SIGNIFICANCE OF CLINICAL AND HISTOLOGICAL PARAMETERS

Sl.no.	Parameter	Responders (n=12)	Non responders (n=9)	P value
1	Mean age (years)	36.08	24.55	0.230
2	Mean Systolic BP (mm. Hg)	157	171	0.190
3	Mean Diastolic BP (mm. Hg)	93	105	**0.016**
4	Mean urine PCR	4.93	6.44	0.081
5	Mean serum creatinine(µmol/L)	605.91	720.66	0.074
6	Mean latency to specific treatment	17.9 days	21.4 days	0.610
7	Average Crescent score	65.75%	92.77%	**0.010**
8	% of glomeruli with fibrous or fibrocellular crescents	26.45%	69.54%	**0.020**
9	Requirement for dialysis	75% (9 out of 12)	100% (9 out of 9)	0.423
10	Preexisting glomerular disease	2	4	0.090

DISCUSSION

A total of seventy nine patients presenting with the syndrome of Rapidly Progressive Glomerulonephritis (RPGN) to the Nephrology department over a period of twenty seven months were identified and subjected to renal biopsy. Renal histology revealed that about 33% of patients (26 out of 79) with RPGN had diffuse crescentic glomerulonephritis, 52% (41 out of 79) had some form of glomerulonephritis (diffuse proliferative/ exudative and proliferative/ mesangio proliferative) with only focal crescent formation and the remaining 15% (12 out of 79) had only diffuse endocapillary proliferation.

The various pathologic conditions which can present with the clinical syndrome of RPGN include diffuse crescentic glomerulonephritis, acute glomerulonephritis with focal crescent formation, diffuse endocapillary proliferation (when severe), acute interstitial nephritis and thrombotic microangiopathy[(1)]. However thrombotic microangiopathy and acute interstitial nephritis were not encountered in the renal biopsy samples studied.

Only the twenty six patients with crescentic glomerulonephritis were included in the study and analyzed for clinical profile, etiology, outcome and prognostic factors.

Demographic characteristics:

The study included included 11 males and 15 females. Children below 12 years of age were excluded from the study. The mean age of the study population was 32.96 years and the age ranged from 14 to 70 years. The mean age of patients in the three different immunopathologic categories of crescentic glomerulonephritis was as follows:

a) Anti GBM nephritis – 14.50 years

b) Immune complex nephritis – 29.16 years

c) Pauci immune nephritis – 50.50 years

Even though Anti GBM nephritis can affect all ages and both sexes, there is a predilection for males in the second decade of life, females in the sixth and seventh decades of life [(2)]. However the study detected one male and one female patient with Anti GBM nephritis, both in their second decades of life. Patients affected by pauci immune nephritis in this study tended to be older with a mean age of 50.50 years. The relative frequency of the three immunopathologic categories of Crescentic glomerulonephritis in different age groups is shown in Box 13. In individuals older than 60 years, pauci immune nephritis was found to be the commonest cause of Crescentic glomerulonephritis. Immune complex glomerulonephritis accounted for the majority of Crescentic glomerulonephritis in individuals younger than 60 years of age, with maximum occurrence between 20 and 60 years of age. Both cases of Anti GBM nephritis affected patients less than 20 years of age.

Box 13: RELATIVE FREQUENCY OF IMMUNOPATHOLOGIC CATEGORIES OF CRESCENTIC GLOMERULONEPHRITIS IN DIFFERENT AGE GROUPS:

Category	Age in years		
	12 – 20 (n = 9)	20 – 60 (n = 13)	> 60 (n = 4)
Anti GBM nephritis	22.2% (2 out of 9)	0% (0 out of 13)	0% (0 out of 13)
Immune complex nephritis	66.6% (6 out of 9)	84.6% (11 out of 13)	25.0% (1 out of 4)
Pauci immune nephritis	11.1% (1 out of 9)	15.4% (2 out of 13)	75.0% (3 out of 4)

Immunopathologic categorization:

Based on the immunofluorescence analysis of the renal biopsy specimen, three categories of crescentic glomerulonephritis were identified. Immune complex nephritis was the most common type observed accounting for 69.2% (18 out of 26) of the cases followed by pauci immune nephritis occurring in 23% (6 out of 26). Anti GBM nephritis was seen in 7.8% (2 out of 26) of the population. This relatively high proportion of immune complex nephritis contrasts with the data from western nations where pauci immune nephritis accounts for the majority (>60%) of crescentic glomerulonephritis[3]. In a retrospective clinico pathologic study of 230 patients with crescentic glomerulonephritis from South India by Anuradha Raman et al., immune complex glomerulonephritis was found to be most common type accounting for 97.4%., followed by Pauci immune nephritis (2.17%) and Anti GBM nephritis (0.17%) [4].

A prospective study of 22 children with crescentic glomerulonephritis from Sanjay Gandhi Post Graduate Institute, Lucknow [5] also reported a similar preponderance of immune complex glomerulonephritis (86.36%) followed by anti GBM nephritis (0.09%) and pauci immune nephritis (0.04%). A similar scenario was reported by M.Vijayakumar et al., in South Indian children with crescentic glomerulonephritis [6].

Etiologic profile of Crescentic Immune complex glomerulonephritis:

Among the various known etiologies of immune complex crescentic glomerulonephritis, lupus nephritis, Post Infectious Glomerulonephritis (PIGN), IgA nephropathy, Henoch Schonlein nephritis and Membranous nephropathy were identified in the study.

Lupus nephritis was found to be the most common cause of immune complex glomerulonephritis accounting for 50% of patients (9 out of 18). PIGN, IgAN and Henoch Schonlein nephritis accounted for 22.2% (4 out of 18), 11.1% (2 out of 18) and 11.1% each respectively. Membranous nephropathy was diagnosed in one patient i.e., 5.6% of patients with immune complex nephritis.

A retrospective clinico pathologic study of Rapidly progressive Renal Failure (RPRF) in 103 patients, conducted at the Department of Nephrology, Madras Medical college in the year 2005 revealed that RPGN accounted for 98% of all cases of RPRF. Among the various causes of RPGN, Immune complex glomerulonephritis was the commonest cause of accounting for 93.2% of all cases of RPGN. Pauci immune nephritis and anti GBM nephritis each accounted for 2.9% and 1.9% of RPGN. Crescents were observed in 60.3% of the patients and Class 4 lupus nephritis was found to be most common cause of crescents [7].

However in several other clinico pathologic studies from India, PIGN was found to be the most common cause of crescentic immune complex nephritis [4, 5, 6]. Lupus nephritis was found to be the next common etiology in adult patients.

The exclusion of pediatric population (< 12 years age) from the present study might explain the preponderance of lupus nephritis. The other quoted studied had included children which might account for a higher proportion of PIGN.

Membranous nephropathy is a rare etiology of crescentic glomerulonephritis. Presence of crescents in membranous nephropathy should prompt search for anti GBM antibodies [14]. Also secondary causes of glomerulonephritis like Lupus nephritis need to be excluded. The present study identified one patient with Crescentic membranous nephropathy in whom ANA (Anti

Nuclear Antibody) testing was done and found to be negative. ANCA and Anti GBM testing was precluded by logistic constraints. Hepatotrophic viral infections were also excluded.

Crescentic transformation of preexisting glomerulonephritis:

In most patients crescentic glomerulonephritis occurred as a denovo manifestation i.e., in patients in whom there was no histological or clinical evidence of preexisting glomerulonephritis. A few patients had preexisting glomerulonephritis - five patients were known to have diffuse proliferative lupus nephritis and one patient had Henoch Schonlein purpura. Out of the five patients with diffuse proliferative lupus nephritis, one patient refused immunosuppressive therapy and was remaining only on supportive measures, three patients had achieved partial remission of proteinuria after institution of Cyclophosphamide pulse therapy, and one patient had been initiated on Cyclophosphamide two months prior to Crescentic transformation. Two of these patients presented to the clinic with diarrhea as the initial manifestation. The occurrence of crescentic transformation in these patients exemplifies the inherent nature of the disease to flare, even while remaining on potent immunosuppressant like Cyclophosphamide. The patient with preexisting Henoch Schonlein purpura was an eighteen years old male who remained in remission before the occurrence of crescentic glomerulonephritis. Scabies antedated crescentic glomerulonephritis in this patient.

Precipitating factors:

Among the known provoking factors for crescentic glomerulonephritis, skin infection was identified in two patients. One patient developed PIGN following insect bite and skin infection. The other patient had preexisting Henoch Schonlein nephritis and scabies preceded the crescentic transformation. It is estimated that infective episodes precede HSP in upto 50% of the cases [(12)].

There was no hydrocarbon exposure or smoking in both the patients with Anti GBM nephritis. No other toxin could be identified in the study.

Renal and extra renal manifestations:

All patients with crescentic glomerulonephritis had edema, but the urine output varied considerably between patients. 30% of patients were anuric and 35% were oliguric while the remaining 35% were nonoliguric at presentation. A similar proportion of nonoliguric presentation was reported by Anuradha Raman et al.,[(4)]. The urine output in crescentic glomerulonephritis depends on several factors like the speed at which crescents develop, the extent of crescent formation and the presence or absence of chronic tubulo interstitial changes. anti GBM nephritis, for instance is characterized by a fulminant presentation with oligo-anuria due to extensive crescent formation, with all the crescents occurring simultaneously. An insidious onset of crescent formation with synchronous involvement of the glomeruli or presence of chronic tubulo interstitial changes which could impair the urinary concentrating ability might account for non oliguric presentation[(10)]. Both the patients with Anti GBM nephritis presented with anuria while the urine output varied in the other two immunopathologic categories. About 27% of the study population had visible haematuria. The urine sediment revealed a nephritic picture in all patients.

Extra renal manifestations differed according to the etiology of crescentic glomerulonephritis. Pulmonary haemorrhage was seen in one patient with Anti GBM nephritis (Goodpasteur Syndrome). Extra renal manifestations were most pronounced in the immune complex nephritis group. About 61% of patients (11 out of 18) with immune complex nephritis had extra renal manifestations like pleurisy, arthralgia, skin rash, seizures, cerebral infarction and

spinal and frontal demyelination. Ante partum haemorrhage occurred in a patient with IgA nephropathy. Palpable purpura and arthralgia were observed in Henoch Schonlein purpura. Patients with lupus nephritis manifested oral ulcers, arthralgia, erythema nodosum, seizures and cerebral infarct.

Out of the six patients with pauci immune nephritis, only one patient had transient arthralgia. No other extra renal manifestations known to occur in systemic vasculitis (like respiratory tract granulomas, airway hyper reactivity, pulmonary haemorrhage, peripheral neuropathy, ocular manifestations, purpura or other deramatologic manifestations) were encountered in the study population. The renal biopsy revealed fibrinoid necrosis of medium sized blood vessel in yet another patient, indicating the systemic nature of the disease. Overall, about 66% (4 out of 6) of patients with pauci immune nephritis had a "renal limited" disease without any of the known systemic manifestations.

Renal-limited forms of pauci immune crescentic glomerulonephritis are thought to be related to small vessel vasculitis with exclusive involvement of the glomerular capillaries [(11)]. This form of renal limited vasculitis was previously referred to as "Idiopathic Crescentic Glomerulonephritis".

Blood Pressure at presentation:

In general hypertension is less severe in crescentic glomerulonephritis [(13)]. Involvement of the juxta glomerular apparatus in the inflammatory process with resultant impairment of renin production is postulated as the mechanism. . In the present study only one patient had a BP less than 140/90 mm Hg. The remaining 25 patients had hypertension to varying degrees. At the time of presentation, 38.5% of the study population had mild to moderate hypertension (defined as BP

141/91 to 160/100 mm Hg) and 42.3% of the population had severe hypertension (defined as BP ≥ 161/101 mm Hg).

Sodium and water retention accounts for hypertension in glomerular diseases. The PRA (Plasma Renin Activity) is suppressed by hypervolemia. Involvement of medium sized blood vessels in systemic vasculitis could result in renal ischemia and account for hypertension in Crescentic glomerulonephritis. The average time to presentation after the onset of symptoms was 13.76 days. All patients had evidence of hypervolemia at presentation and the average serum creatinine at entry was 642μmol/L. Moreover 34.6% (9 out of 26) of the patients had pre existing hypertension. These factors could have contributed to severe hypertension that was seen in 42.3% of the study population.

The average blood pressure at presentation, according to the immunopathologic categories was found to be highest in immune complex glomerulonephritis (170.6/99.6 mm Hg) followed by anti GBM nephritis (163.0/105.0 mm Hg) and pauci immune nephritis (152.6/91.6 mm Hg).

A few confounding factors with respect to interpretation of blood pressure, like pregnancy and liver disease were noted. These states tend to lower the BP themselves and even a marginally elevated BP may be considered equivalent to severe hypertension. These caveats need consideration in evaluating the prognostic significance of hypertension in crescentic glomerulonephritis.

Urine protein excretion at presentation:

The highest mean urine protein excretion (urine PCR) at presentation, was recorded in anti GBM nephritis (6.30), followed by immune complex nephritis (5.92) and pauci immune nephritis (3.46). The difference in urine protein excretion between anti GBM nephritis and pauci

immune nephritis, immune complex nephritis and pauci immune nephritis each reached statistical significance implying that urine protein excretion was significantly higher in anti GBM nephritis and immune complex nephritis.

High grade proteinuria usually occurs in immune complex glomerulonephritis among the three immunopathologic categories. Proteinuria tends to be modest in anti GBM nephritis and Pauci immune nephritis. However highest proteinuria in this study was recorded in anti GBM nephritis. The small sample size (two patients) of anti GBM nephritis needs to be considered before drawing final conclusions in this regard.

Serologic profile of Crescentic glomerulonephritis:

The serologic findings of crescentic glomerulonephritis are summarized in Box 4 through Box 8. Circulating anti GBM antibodies were detectable in both patients with anti GBM nephritis. One patient with histologic features of anti GBM nephritis also had circulating P – ANCA (double positive). Such double positive patients are reported in literature and may have a clinical course and response to treatment more typical of vasculitis than anti GBM disease. Anti GBM disease in such patients develop probably due to vasculitic glomerular damage and the ANCA detectable is P – ANCA [(15)].

Out of the nine patients who had immunofluorescence feature and complement profile suggestive of lupus nephritis (both C3 and C4 low), ANA(anti nuclear antibody) was tested in seven patients and found to be positive in five patients and negative in the remaining two (Fig.10). Anti double stranded DNA (Anti ds DNA) was tested in six patients and found to be positive in five patients. ANA are present in about 90% of untreated lupus patients [(16)]. Thus, nearly 10% of patients with active lupus could test negative for circulating ANA. In the present

study, about 28% (2 out of 7) of patients with crescentic lupus nephritis were found to be ANA negative. Anti ds DNA antibodies imply active renal disease, but lack sensitivity. About 83% (5 out of 6) of patients with crescentic lupus nephritis tested positive for anti ds DNA antibodies.

Out of the four patients with PIGN (diagnosis based on immunopathology and complement profile) ASO titer was tested in two patients and found to be positive in one patient. A study found elevated ASO titers in only one-third of the patients, while anti-DNAse titres were high in 73 per cent of postimpetigo cases[17]. The streptozyme test, which includes four antigens (DNAse B, Streptolysin O, hyaluronidase, and streptokinase), is elevated in nearly 80 per cent of the cases. The patient who tested negative also developed spinal and frontal demyelination from which she made a complete recovery in a month's period. Demyelination in this patient could also be secondary to infection. Circulating ANA was detectable in one patient with PIGN.

ANCA (P and C) were tested in all six patients with Pauci immune nephritis. P – ANCA was detectable in two patients while none had C – ANCA. In the present study only two patients had systemic manifestations as previously mentioned. The remaining four patients had renal limited vasculitis. It is estimated that about 80% patients with renal limited vasculitis are P – ANCA positive [18]. However in the present study only 33.33% of patients were ANCA positive. Out of the two patients who were P –ANCA positive, one had renal limited vasculitis and the other had extra renal manifestation in the form of arthralgia. The patient with fibrinoid necrosis of medium sized blood vessel (and thus systemic small vessel vasculitis) did not have circulating ANCA. The clinical presentation and response to treatment of such ANCA negative systemic vasculitis closely resemble ANCA positive vasculitis [19].

Pregnancy and Crescentic glomerulonephritis:

Crescentic glomerulonephritis is a rare cause of renal failure in pregnancy [20]. Reports of Anti GBM nephritis [21] and Pauci immune crescentic nephritis [22] during pregnancy are available in literature. Pregnancies invariably ended in fetal loss. The renal outcome on the other hand, varied from one patient to other. While renal function improved after termination of pregnancy and immunosuppressive therapy in some patients, others had a relentless progression to ESRD.

The present study identified two patients with crescentic glomerulonephritis occurring during pregnancy. One patient had PIGN, presented during second gestation at 8 months amenorrhea with RPGN and dialysis requiring renal failure. Pregnancy was terminated and IV followed by oral corticosteroid administered. Renal function recovered completely by one month.

The other patient was a primi who presented at 8 months amenorrhea with antepartum haemorrhage and dialysis requiring renal failure. Pregnancy was terminated and biopsy revealed Crescentic IgA nephropathy. Late presentation and severe chronic lesions in biopsy precluded immunosuppressive therapy. This patient landed up with ESRD and died of pulmonary edema by third month due to non compliance with dialysis.

Short term outcome of Crescentic glomerulonephritis:

As previously summarized in Box 9 & 10 and Fig.15 & 16, at three months, out of the 26 patientswith crescentic glomerulonephritis, 5 patients lost follow up, 2 patients were dead, 7 patients remained dialysis dependent (ESRD) and the remaining 12 patients had complete or partial recovery of renal function and remained free of dialysis. Thus the outcome was “adverse” (death or ESRD) in 34.16% (9 out of 26) of patients with crescentic glomerulonephritis.

46.15% (12 out of 26) of patients were dialysis independent at 3 months. The average serum creatinine at three months in this subgroup was 213.58μmol/L. In 4 of these patients, renal function approached baseline with creatinine falling less than 1.5 mg/dl (132μmol/L). At 3 months the average urine PCR was 2.125 in those remained dialysis free. Partial remission of proteinuria was seen in 10 out of 12 patients (83.33%) while 2 patients failed to achieve any remission of proteinuria. None had a complete remission of proteinuria at 3 months.

The outcome differed according to the immunopathologic categories. Patients with Anti GBM nephritis had the worst short term outcomes, with 50% mortality and 50% developing ESRD. No mortality occurred in those with Pauci immune nephritis and all the 4 patients who were still following up at 3 months were dialysis independent. In other words no "adverse" outcome befell patients with Pauci immune nephritis. Patients with immune complex nephritis had both "favorable" and "adverse" outcomes. out of the 15 patients who followed up at third month, 33.33% developed ESRD, 5.55% died, 22.22% had complete recovery of renal function with creatinine falling less than 132 μmol/L and 22.22% had partial recovery of renal function (patient dialysis independent).

The Indian scenario of anti GBM nephritis was previously studied by M. Ahmad et al., form Sanjay Gandhi Post Graduate Institute, Lucknow [(23)]. Out of the 18 patients studied nearly one third had pulmonary haemorrhage and 7 patients were considered eligible for immunosuppression and plasmapheresis. 4 patients recovered renal function after specific therapy. In the present study, both the patients had adverse short term outcome – one patient developed ESRD and the other died due to respiratory insufficiency from pulmonary haemorrhage. Presentation with advanced renal failure and pulmonary haemorrhage could have contributed to the dismal outcome in this subgroup.

A retrospective study of anti GBM nephritis over 12 years period (1988 – 1999) was performed at the Department of Nephrology, Madras Medical College. 12 patients with anti GBM nephritis were identified and anti GBM nephritis was found to contribute to 10% of all Crescentic glomerulonephritis. A similar fulminant presentation with 25% of patients manifesting pulmonary haemorrhage was noted. The outcome was bleak with about 50% short term mortality.

The outcome of crescentic immune complex glomerulonephritis varied according to the etiology. Two patients with crescentic IgA nephropathy were identified in the present study. One patient was treated with pulse steroids and IV Cyclophosphamide and immunosuppression was deferred in the other considering the late presentation and advanced sclerosing lesions in histology. Both patients developed ESRD and one of them died due to non compliance with dialysis. PIGN was observed in 4 patients, one was lost to follow up, and one developed ESRD over short term, two patients recovered. Out of the 9 patients with crescentic lupus nephritis, 5 patients (55.55%) recovered renal function and remained dialysis independent at 3 months of follow up, 3 patients (33.33%) developed ESRD and one was lost to follow up. One patient with crescentic membranous nephropathy progressed to ESRD. Two patients with crescentic Henoch Schonlein nephritis remained dialysis independent at 3 months.

In a large prospective study of 93 patients with lupus nephritis and crescents, with follow up lasting more than 50 months from China [(24)], at third month follow up almost all patients were documented to have improvement in renal function and proteinuria. However only 62% of these patients presented with RPGN and only 15% required dialysis.all patients received induction with pulse steroids and IV Cyclophosphamide in this study.

In the present study included only patients with diffuse crescentic glomerulonephritis and only one out of 9 patients with crescentic lupus nephritis did not require dialysis. These characteristics could account for the low remission rate of 55.55% at 3 months noted in the present study.

Among the 6 patients with pauci immune nephritis in the present study, there was no short term mortality and none required dialysis at 3 months. However two patients were lost to follow up at third month. One patient had recovered renal function by one month and became dialysis independent. The other patient remained dialysis dependent at one month and was lost to follow up at three months.

The outcome in pauci immune nephritis has improved after the use of Cyclophosphamide and plasmapheresis for induction. Remission rates following induction treatment vary from 35 – 93% in Wegeners Granulomatosis and 75 – 89% in Microscopic polyangiitis [25]. In the present study most patients (4 out of 6) had renal limited vasculitis and most (4 out of 6) were ANCA negative. The confinement of disease to renal microcirculation without any threatening manifestations like pulmonary haemorrhage was a favorable feature noted in the present study.

Prognostic factors in Crescentic glomerulonephritis:

The short term outcome in crescentic glomerulonephritis depends on several clinical and histologic factors. Poor prognostic factors identified in the present study include diastolic BP ≥ 105 mm Hg, a crescent score ≥ 92.77% and involvement of atleast 69.5% of the sampled glomeruli by fibrous or fibro cellular crescents.

Presence of severe tubular atrophy and interstitial fibrosis, glomerular tuft necrosis are other known predictors of poor outcome in crescentic glomerulonephritis [1]. In the present study

chronic tubulo interstitial lesions were graded as mild, moderate, severe and none. Exact quantification in numerical terms, as percentage of interstitium involved was not done and this precluded statistical comparison between responders and non responders. In qualitative terms, about 42% of the responders had no chronic tubulo interstitial changes and the remaining 58% of patients had mild chronic tubulo interstitial changes. Among the non responders, 55.55% had mild, 33.33% had moderate and 11.11% had severe chronic tubulo interstitial changes. Thus moderate and severe chronic tubulo interstitial changes were noted among non responders.

Glomerular tuft necrosis was observed in two patients in the present study. One had anti GBM nephritis and pulmonary haemorrhage and the other Pauci immune nephritis. Both had advanced renal failure and required plasmapheresis. The one with Goodpasteur syndrome died and the other patient defaulted at one month when she was still dialysis dependent.

Other parameters like age, systolic BP, proteinuria and serum creatinine at presentation, the average time to institution of specific treatment and requirement for dialysis were tested as prognostic factors. But none of these factors could predict outcome and failed to qualify as prognostic markers in the present study.

CONCLUSION

1) Crescentic glomerulonephritis was found to be equally distributed among both sexes in adults.
2) In most patients, crescentic glomerulonephritis occurred as a denovo manifestation, while a few others had pre existing glomerulonephritis like lupus nephritis and Henoch Schonlein nephritis.
3) Fever, diarrhea, respiratory and skin infection preceded crescentic glomerulonephritis in majority (53%) of patients.
4) Major symptoms at presentation included oliguria, anuria and haematuria. About 35% of the patients had a non oliguric presentation.
5) Extra renal manifestations were pronounced in immune complex nephritis and anti GBM nephritis, while most of the patients (66%) with pauci immune nephritis had a renal limited disease.
6) Hypertension was seen in all but one patient and about 42% of the patients had severe hypertension (BP $\geq$ 161/101 mm Hg).
7) Immune complex nephritis was the predominant immunopathologic category of crescentic glomerulonephritis accounting for about 69% of all cases, followed by pauci immune nephritis (23% of cases) and Anti GBM nephritis (8% of cases).
8) A half of immune complex glomerulonephritis was due to Lupus nephritis. PIGN accounted for 22%, IgA nephropathy and Henoch Schonlein purpura for 22% and membranous nephropathy accounted for 6% of immune complex nephritis.

9) Urine protein excretion was highest in Anti GBM nephritis and lowest in Pauci immune nephritis. Mean urine protein excretion was in the nephrotic range in both Anti GBM nephritis and Immune complex nephritis.
10) Most patients with pauci immune nephritis were ANCA negative. Only P – ANCA was detectable in the study population. One patient was "double positive" and had both circulating Anti GBM antibody and P – ANCA.
11) On an average 77.46% of the glomeruli revealed crescents. All ages of crescents were seen. Glomerular tuft necrosis was seen in 11.5% of the patients.
12) About 88% of patients required dialysis. Mean serum creatinine at presentation was 642μmol/L.
13) IV and oral steroids, Cyclophosphamide and plasmapheresis were employed as treatment modalities.
14) Mean latency between symptom onset and specific treatment was 17.45 days.
15) At three months about 7.6% died, 27% remained dialysis dependent (ESRD), 46% had partial or complete recovery of renal function and remained dialysis free and 19.5% were lost to follow up.
16) Outcome was worst in Anti GBM nephritis with 50% mortality and 50% ESRD.
17) Pauci immune nephritis had the best outcome with none dying or remaining dialysis dependent.
18) Outcome was mixed in immune complex nephritis with 33% mortality, 44% recovering renal function and about 5% developing ESRD.

19) Poor prognostic factors identified in the present study include diastolic BP ≥ 105 mm Hg, a crescent score ≥ 92.77% and involvement of atleast 69.5% of the sampled glomeruli by fibrous or fibro cellular crescents.

CRESCENTIC GLOMERULONEPHRITIS

Sl. no	Name	Crescent		Tuft necrosis	Capillary walls	Endocapillary proliferation	TA/IF	Interstitial inflammation	Blood vessels	Immunofluorescence
		%	Age							
1	Vignesh	50	C	none	*	DPGN	none	mild	normal	Gr, P, M, fullhouse
2	Narayanan	100	FC	none	*	*	mild	mild	normal	No significant deposits
3	Suresh	66	C	none	normal	Mes. Prolif.	mild	none	Thickened	M , IgA
4	Mumtaj	80	C	none	Thick	DPGN	none	Diffuse	normal	Gr, P, M, fullhouse
5	Sambasivam	100	C	none	*	Exud .Prolif	none	mild	normal	Gr, M, P, IgG
6	Munusamy	70	FC	none	*	*	mild	Dense patchy	normal	No significant deposits
7	Rajammal	90	C	none	*	Exud .Prolif	none	none	normal	Gr, M, P, IgG,IgM,C3
8	Periyandavar	50	C	none	*	Exudation	none	Dense patchy	Fibrinoid necrosis	No significant deposits
9	Elumalai	100	FC,C	none	Thick	*	mild	Diffuse	Thickened	Gr, M, P, IgG,IgM
10	Ramanibai	50	C	none	normal	Mes. Prolif.	none	mild	Thickened	M , IgA
11	Dharman	80	FC,C	none	Thick/spikes	none	mod	dense	normal	Gr, P, IgG, IgM
12	Karthik	100	FC	Present	*	*	mod	mild	normal	L, IgG
13	Shanthi	90	C	none	*	DPGN	mild	Dense patchy	Thickened	Gr, P, M, fullhouse
14	Balakrishnan	80	C	none	*	*	mild	mild	normal	No significant deposits
15	Jayamani	68	C	none	normal	Mes. Prolif	mild	mild	Thickened	No significant deposits
16	Feroz khan	100	FC	none	*	DPGN	mild	Dense	Thickened	Gr, P, M, fullhouse
17	Valliammal	80	C,FC	Present	Fibrin seen	*	none	Diffuse	normal	No significant deposits
18	Nirmala	60	C	none	*	Exud .Prolif	none	diffuse	normal	Gr, P, M IgM, C3
19	Ezhilarasi	60	C,FC	None	Reduplicated	Exud .Prolif	mild	mild	Thickened	Gr, P, M, fullhouse
20	Shaheen	50	C	none	Thick	DPGN	mild	mild	Thickened	Gr, P, M, fullhouse
21	Nooriya zarith	75	FC	none	*	Mes. Prolif	severe	Dense patchy	Thickened	M , IgA
22	Umesh	70	C,FC	none	*	Mes. Prolif	mod	mild	Thickened	M , IgA
23	Jayanthi	100	FC	none	Thick	DPGN	mod	mild	Thickened	Gr, P, M, fullhouse
24	Kavitha	100	F	Present	*	*	mild	mild	normal	L, IgG
25	Soundarya	55	C	none	Thick	DPGN	mild	Dense patchy	Thickened	Gr, P, M, fullhouse
26	Kalaimathy	90	F	none	Thick	DPGN	severe	mild	Thickened	Gr, P, M, fullhouse

F = Fibrous; FC = FibroCellular; C= Cellular; * = not discernable; TA = Tubular Atrophy; IF = Interstitial Fibrosis; Gr = GranularL=Linear; M=Mesangial; P=peripheral ; Mes.Prolif = Mesangial Proliferation; IgAN = IgA Nephropathy; Exud.Prolif=Exudative proliferation; mod = moderate;

CRESCENTIC GLOMERULONEPHRITIS

Sl. no	Name	Urine PCR	Urine sediment	HB gm %	TC	Platelets Lakh/µl	Entry Creat. µmol/l	Chest/ sinus/ other imaging	C3	C4	ANA	Anti ds DNA	Anti GBM	ASO	ANCA		HIV HCV HBV
															p	c	
1	Vignesh	4.70	Nephritic	9.0	7400	1.9	350	n	↓	↓	pos	pos	---	---	neg	neg	neg
2	Narayanan	3.60	Nephritic	6.5	5900	2.4	2413	n	n	n	neg	---	---	---	neg	neg	neg
3	Suresh	8.63	Nephritic	10.6	6200	2.5	335	n	n	n	---	---	---	neg	---	---	neg
4	Mumtaj	4.74	Nephritic	7.8	4200	1.4	215	n	↓	↓	neg	neg	---	neg	---	---	neg
5	Sambasivam	5.80	Nephritic	10.2	9100	2.6	512	n	---	---	---	---	---	---	---	---	neg
6	Munusamy	2.22	Nephritic	7.8	11200	1.8	627	Lt lacunar infarct	n	n	---	---	---	---	neg	neg	neg
7	Rajammal	5.82	Nephritic	10.2	5200	2.8	510	Demyelin.	↓	n	neg	---	---	neg	---	---	neg
8	Periyandavar	4.06	Nephritic	13.8	6700	3.0	673	n	n	n	neg	---	---	---	neg	neg	neg
9	Elumalai	8.80	Nephritic	7.2	12800	3.0	2154	n	↓	n	neg	---	---	---	neg	neg	neg
10	Ramanibai	4.80	Nephritic	8.0	18800	3.5	693	cardiomegaly	n	n	neg	---	---	---	neg	neg	neg
11	Dharman	5.20	Nephritic	10.5	8700	4.2	509	n	n	n	neg	---	---	---	---	---	neg
12	Karthik	8.80	Nephritic	8.5	10800	2.6	745	B/L lung opacities	n	n	neg	---	pos	---	pos	neg	neg
13	Shanthi	5.40	Nephritic	5.2	4600	2.0	130	n	↓	↓	---	---	---	---	---	---	neg
14	Balakrishnan	4.50	No RBCs	11.0	7000	2.2	590	n	n	n	---	---	---	---	neg	neg	neg
15	Jayamani	3.60	Nephritic	9.2	7400	2.6	281	n	n	n	neg	---	---	neg	**pos**	neg	neg
16	Feroz khan	4.8	Nephritic	5.5	4300	1.2	344	n	↓	↓	pos	pos	---	---	---	---	neg
17	Valliammal	2.80	Nephritic	6.8	6700	2.2	1320	n	n	n	---	---	---	---	**pos**	neg	neg
18	Nirmala	4.30	Nephritic	5.6	11200	2.0	400	n	↓	n	pos	---	---	pos	---	---	neg
19	Ezhilarasi	4.70	Nephritic	5.8	11800	1.8	446	n	↓	↓	neg	---	---	---	---	---	HBSAg +,e- ve
20	Shaheen	3.86	No RBCS	8.0	7600	2.0	287	Pericard. Eff.	↓	↓	pos	---	---	---	---	---	neg
21	Nooriya zarith	5.76	Nephritic	7.8	6800	3.6	498	n	---	---	neg	---	---	---	---	---	neg
22	Umesh	6.20	Nephritic	7.9	10400	2.3	452	n	n	n	neg	---	---	neg	---	---	neg
23	Jayanthi	6.80	Nephritic	6.8	4700	2.1	654	n	↓	↓	pos	pos	---	---	---	---	neg
24	Kavitha	3.80	Nephritic	7.4	5400	2.9	784	n	n	n	neg	---	pos	---	neg	neg	neg
25	Soundarya	8.50	Nephritic	9.2	13800	1.0	435	Lt MCA infarct	↓	↓	pos	pos	---	---	---	---	neg
26	Kalaimathy	7.80	Nephritic	8.4	6400	2.6	346	Psoas absces	↓	↓	pos	pos	---	---	---	---	neg

n =normal; neg = negative; --- = not done; Lt =left; ↓= low; pos =positive; Demyelin. = demyelination C4 & right frontal region in MRI

CRESCENTIC GLOMERULONEPHRITIS

Sl. no	Name	Age/ sex	Presenting symptoms					Prodromal/Preceding events			Antecedent problems		
			edema	oliguria	anuria	hematuria	Duration	RTI	fever	Drug/toxin/others	HT	DM	others
1	Vignesh	15M	+	-	-	+	15 days	-	-	-	-	-	-
2	Narayanan	47M	+	+	+	+	30 days	-	-	Smoking (40py)	-	-	-
3	Suresh	18M	+	-	-	-	7 days	-	-	Scabies	+	-	HSP
4	Mumtaj	26F	+	+	-	-	30 days	-	-	-	-	-	-
5	Sambasivam	60M	+	+	-	+	14 days	-	-	Insect bite,drugs(?)	-	-	-
6	Munusamy	70M	+	-	-	-	11 days	-	+	Envas, Sumo	+	-	CVA
7	Rajammal	40F	+	+	-	+	5 days	-	+	GTCS – 7 episodes	-	-	-
8	Periyandavar	35M	+	-	-	+	14 days	-	-	-	-	-	DCLD/PHT/varices
9	Elumalai	63F	+	+	+	-	35 days	+	+	Smoking (25 py)	-	-	-
10	Ramanibai	52F	+	+	+	-	3 days	-	-	Amlodipine	+	-	Rash
11	Dharman	33M	+	-	-	-	20 days	-	-	-	-	-	Edema – 1 year
12	Karthik	15M	+	+	+	-	7 days	-	+	-	-	-	-
13	Shanthi	26F	+	+	-	-	20 days	-	-	-	+	-	K/C/O Class 4 LN, refused therapy
14	Balakrishnan	18M	+	-	-	-	8 days	-	+	Antipyretic (?drug)	-	-	-
15	Jayamani	68F	+	-	-	-	14 days	-	+	Filarial lymphangitis/DEC	-	-	K/C/O filarial leg
16	Feroz khan	16M	+	+	+	-	3 days	-	-	-	+	-	K/C/O Class 4 LN, on NIH, 3 pulses over
17	Valliammal	65F	+	+	+	-	6 days	-	+	Diarrhea, drugs(?)	-	-	-
18	Nirmala	27F	+	+	-	-	7 days	-	-	2nd pregnancy, 8MA	-	-	No PIH in 1st pregn.
19	Ezhilarasi	30F	+	+	-	+	10 days	-	+	Fever – 20 days	-	-	2 spontaneous abortions
20	Shaheen	17F	+	+	-	-	10days	-	+		+	-	K/C/O Class 4 LN,NIH completed , partial rem
21	Nooriya zarith	23F	+	-	-	-	25 days	-	-	1st pregnancy, 8MA	-	-	-
22	Umesh	25M	+	+	-	-	24 days	-	-	-	-	-	-
23	Jayanthi	17F	+	+	+	-	5 days	-	+	Diarrhea	+	-	K/C/O Class 4 LN, on NIH , partial remission
24	Kavitha	14F	+	+	+	+	15 days	+	+	-	-	-	-
25	Soundarya	15F	+	-	-	-	12 days	-	-	-	+	-	
26	Kalaimathy	22F	+	+	-	-	8 days	-	-	Diarrhea	+	-	K/C/O Class 4 LN,NIH completed , partial rem

RTI = Respiratory Tract Infection; + =present; - =absent HT = Hypertension; DM = Diabetes mellitus; CVA = Cerebro Vascular Accident

CRESCENTIC GLOMERULONEPHRITIS

Sl. no	Name	Extra renal symptoms				Clinical examination	
		rash	arthralgia	hemoptysis	Others	BP	General & systemic examination
1	Vignesh	-	+	-	Oral ulcers,seizures	200/110	Gen. lymphadenopathy, oral ulcers, minor jt. arthritis
2	Narayanan	+	-	-	-	140/90	Fixed drug eruption, cheilitis, Rt residual Bells palsy
3	Suresh	-	+	-	-	110/70 (d)	Scabies
4	Mumtaj	-	-	-	Excess hair loss	140/80	Nil specific
5	Sambasivam	-	-	-	-	156/90	Nil specific
6	Munusamy	-	-	-	Myalgia	160/100	Right hemiparesis(residual) power 4/5
7	Rajammal	-	-	-	weakness LL &LUL	160/100	Pyramidal weakness of both LL & LUL
8	Periyandavar	-	-	-	-	120/80	Ascites, hepatosplenomegaly, distended veins
9	Elumalai	-	-	-	wheezing	210/120	Nil specific
10	Ramanibai	+	-	-	-	150/90 (d)	Palpable purpura over lower limbs, evanescent
11	Dharman	-	-	-	-	170/110	Nil specific
12	Karthik	-	-	+(1 month)	Cough – 1 month	170/120	RS: B/L coarse crepitations
13	Shanthi	-	+	-	-	120/80 (d)	Nil specific
14	Balakrishnan	-	-	-	-	200/100	Nil specific
15	Jayamani	-	+	-	-	156/90	Lymphedema left lower limb
16	Feroz khan	+	+	-	-	130/80 (d)	Hyperpigmented macules over trunk & limbs
17	Valliammal	-	-	-	-	140/90	Nil specific
18	Nirmala	-	-	-	-	160/96	Uterus 32 weeks, FH heard
19	Ezhilarasi	-	-	-	-	150/90	Nil specific
20	Shaheen	+	-	-	pleurisy	180/100	Erythema nodosum, pleuritis, pericardial effusion
21	Nooriya zarith	-	-	-	Antepartum haemorrhage at 8MA	140/100	Uterus involuted
22	Umesh	-	-	-	-	166/100	Nil specific
23	Jayanthi	-	+	-	-	170/100	Nil specific
24	Kavitha	-	-	-	-	156/90	Nil specific
25	Soundarya	-	+	-	Seizures	170/100	Nil specific
26	Kalaimathy	-	+	-	Seizures	186/100	Nil specific

- = absent; + = present; (d) = with anti hypertensive drugs; LL = Lower limbs; LUL = Left upper limb

Sl.no	Name	Final diagnosis (Etiology)	Time to specific Rx from onset of symptoms	whether dialysis required	Treatment given			Outcome			
					Steroid	Cyclo.	Plasmapheresis MMF/others	Creatinine (µmol/l)		Urine PCR	
								3 mon	6mon	3mon	6mon
1	Vignesh	Lupus nephritis	24 days	No	IV /PO	IV	none	65	74	2.3	2.2
2	Narayanan	Vasculitis – renal limited	38 days	Yes	IV/PO	PO	none	273	*	1.6	*
3	Suresh	Henoch Schonlein nephritis	13 days	No	PO	PO	none	128	169	3.8	4.6
4	Mumtaj	Lupus nephritis	7 days	yes	IV/PO	IV	none	178	Exp.	2.1	Exp.
5	Sambasivam	PIGN	20 days	yes	IV/PO	-	none	*	*	*	*
6	Munusamy	Vasculitis –renal limited	--	yes	-	-	none	336	293	1.2	1.1
7	Rajammal	PIGN	9 days	yes	IV/PO	-	none	495	170	4.6	1.5
8	Periyandavavar	Vasculitis/DCLD	--	yes	-	-	-	286	174	1.8	1.1
9	Elumalai	PIGN	27 days	yes	IV/PO	-	-	Dial.	Dial.	Dial.	Dial.
10	Ramanibai	Henoch Schonlein nephritis	10 days	yes	IV/PO	-	none	242	*	2.4	*
11	Dharman	Membranous nephropathy	--	yes	-	-	-	Dial.	*	Dial.	*
12	Karthik	Anti GBM disease	35 days	yes	IV/PO	PO	Plasmapheresis	Exp.	Exp.	Exp.	Exp.
13	Shanthi	Lupus nephritis	15 days	yes	IV/PO	IV	-	*	*	*	*
14	Balakrishnan	Vasculitis – renal limited	15 days	Yes	IV/PO	PO	-	*	*	*	*
15	Jayamani	Vasculitis – renal limited	7 days	No	PO	PO	-	186	*	1.3	*
16	Feroz khan	Lupus nephritis	5 days	yes	IV/PO	IV	-	Dial.	Dial.	Dial.	Dial.
17	Valliammal	Vasculitis – renal limited	10 days	yes	IV/PO	PO	Plasmapheresis	*	*	*	*
18	Nirmala	PIGN	9 days	yes	IV/PO	-	Pregnancy terminated	*	*	*	*
19	Ezhilarasi	Lupus nephritis	16 days	Yes	IV/PO	IV	-	112	90	1.2	2.8
20	Shaheen	Lupus nephritis	10 days	Yes	IV/PO	-	MMF	148	*	1.4	*
21	Nooriya zarith	IgA nephropathy	--	Yes	-	-	Pregnancy terminated	Exp.	Exp.	Exp.	Exp.
22	Umesh	IgA nephropathy	30 days	yes	IV/PO	PO	-	Dial.	Dial.	Dial.	Dial.
23	Jayanthi	Lupus nephritis	10 days	yes	IV/PO	IV	-	Dial.	Dial.	Dial.	Dial.
24	Kavitha	Anti GBM disease	--	yes	--	-	-	Dial.	*	Dial.	*
25	Soundarya	Lupus nephritis	39 days	Yes	IV/PO	IV	-	114	*	1.8	*
26	Kalaimathy	Lupus nephritis	--	Yes	-	-	-	Dial.	Exp.	Dial.	Exp.

* = no followup; Exp. = Expired; PIGN= Post Infectious Glomerulo Nephritis; - = not given; -- = not applicable; Dial. = Dialysis dependent

OUTCOME AT ONE MONTH FOR THOSE PATIENTS WHO WERE THEN LOST FOR FOLLOWUP

SL.NO	NAME	RENAL FUNCTION/ CREATININE	EXTRA RENAL MORBIDITY
5	Sambasivam	Dialysis dependent	None
13	Shanthi	Dialysis dependent	None
14	Balakrishnan	creatinine = 428 µmol/l, dialysis independent	None
17	Valliammal	Dialysis dependent	None
18	Nirmala	Creatinine = 93 µmol/l, dialysis independent	None

DETAILS OF PATIENTS WHO WERE MANAGED WITHOUT IMMUNOSUPPRESSION

Sl.no	Name	Diagnosis	Reason for avoiding immunosuppression	Outcome			
				Creatinine(µmol/l)		Urine PCR	
				3 months	6 months	3months	6 months
6	Munusamy	Vasculitis –renal limited	Pyelonephritis	336	293	1.8	1.3
8	Periyandavar	Vasculitis /DCLD	DCLD, portal hypertension & esophageal varices	286	174	1.8	1.1
11	Dharman	Membranous nephropathy	Late presentation	Dialysis dependent	*	Dialysis dependent	*
21	Nooriya zarith	IgA nephropathy	Late presentation , chronic tubulo interstitial changes in biopsy, deranged LFT	expired	expired	expired	expired
24	Kavitha	Anti GBM nephritis	Late presentation	Dialysis dependent	*	Dialysis dependent	*
26	Kalaimathy	Lupus nephritis	Late presentation , chronic tubulointerstitial changes & fibrous crescents in biopsy	Dialysis dependent	expired	Dialysis dependent	expired

DCLD = Decompensated liver disease; * = No follow up

A study of Crescentic Glomerulonephritis – Etiology, clinical presentation, outcome & prognostic factors:

Name:	Age/sex:	NC.No:	DOA:

Presenting Symptoms:

Edema	
Oliguria	
Haematuria	
Extrarenal symptoms	
Duration of symptoms	

Past medical history:

Diabetes mellitus	
HT	
Jaundice	
Edema, haematuria	

Smoking	
Alcohol use	
Obstetric history	

Examination:

Edema		Pulse	
Pallor		BP	
Icterus		RR	
Lymphnodes		Temp	
Skin		CVS	
ENT		RS	
Eyes		Abdomen	
Fundus		CNS	
Bone & joints			

Diagnosis:

Investigations:
Urine:

Blood:

Hb		Serologic workup for RPGN:
Platelet count		
BT,CT		
Peripheral smear		
PT & INR		
Serum Na+ / K+		
Serum cholesterol		
Serum Bilirubin		
SGOT/SGPT		

Renal function:

Others:

CXR /CT Thorax:	
USG Abdomen:	
Xray PNS/ CT PNS:	
Others:	

Renal Biopsy:

Treatment :

Outcome:

1 month	3 months	6 months	

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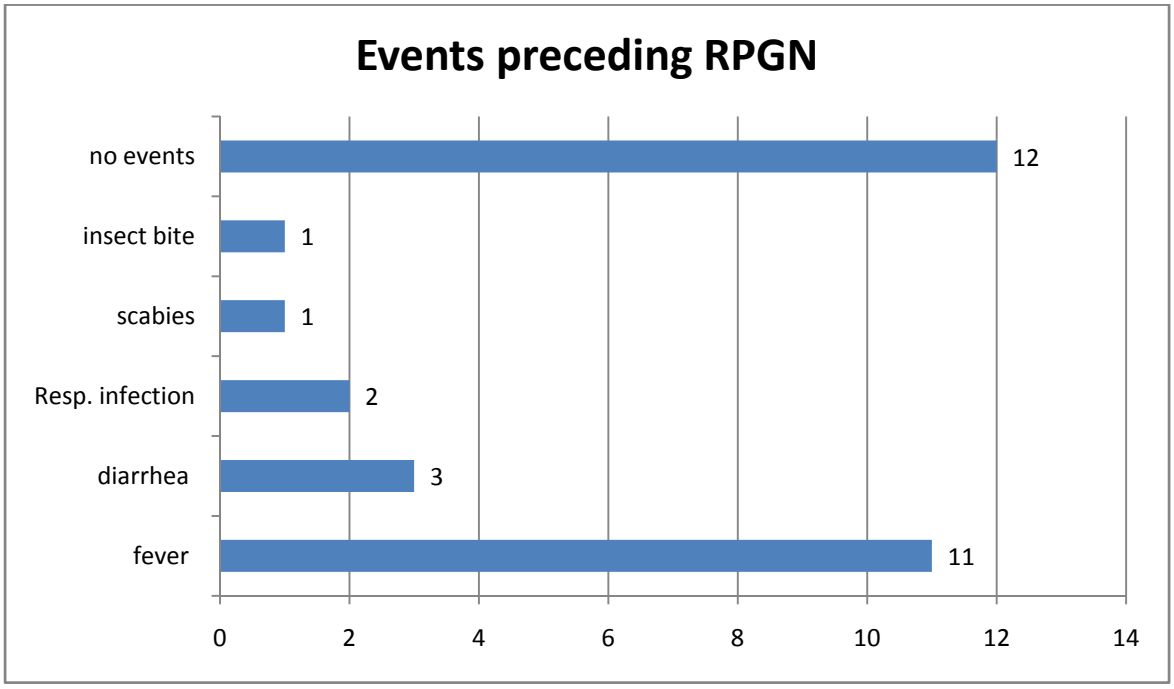


Figure 1: X axis represents the number of patients; events preceding the occurrence of RPGN are marked along the Y axis. Fever with or without diarrhea/respiratory infection appears to be the most common prodromal manifestation

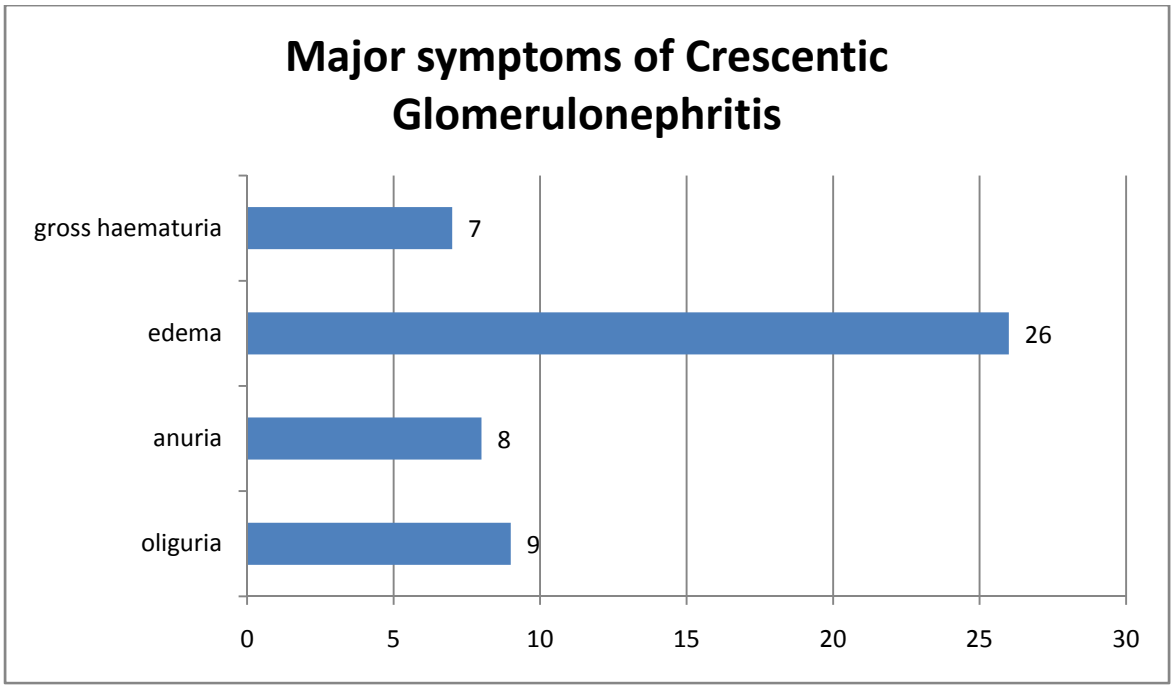


Figure 2: X axis represents the number of patients; major symptoms at clinical presentation are plotted along the Y axis

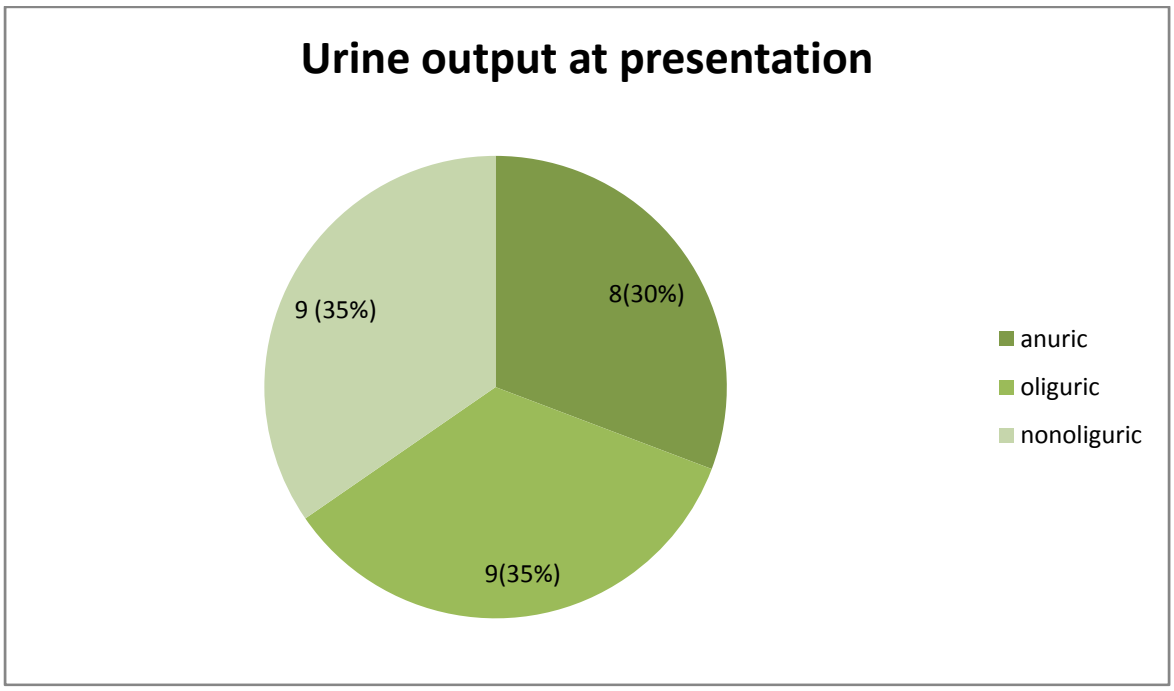


Figure 3: Oliguric, anuric and nonoliguric presentations of Crescentic Glomerulonephritis. Numbers within each sector represents the number of patients (% of total population) in each category

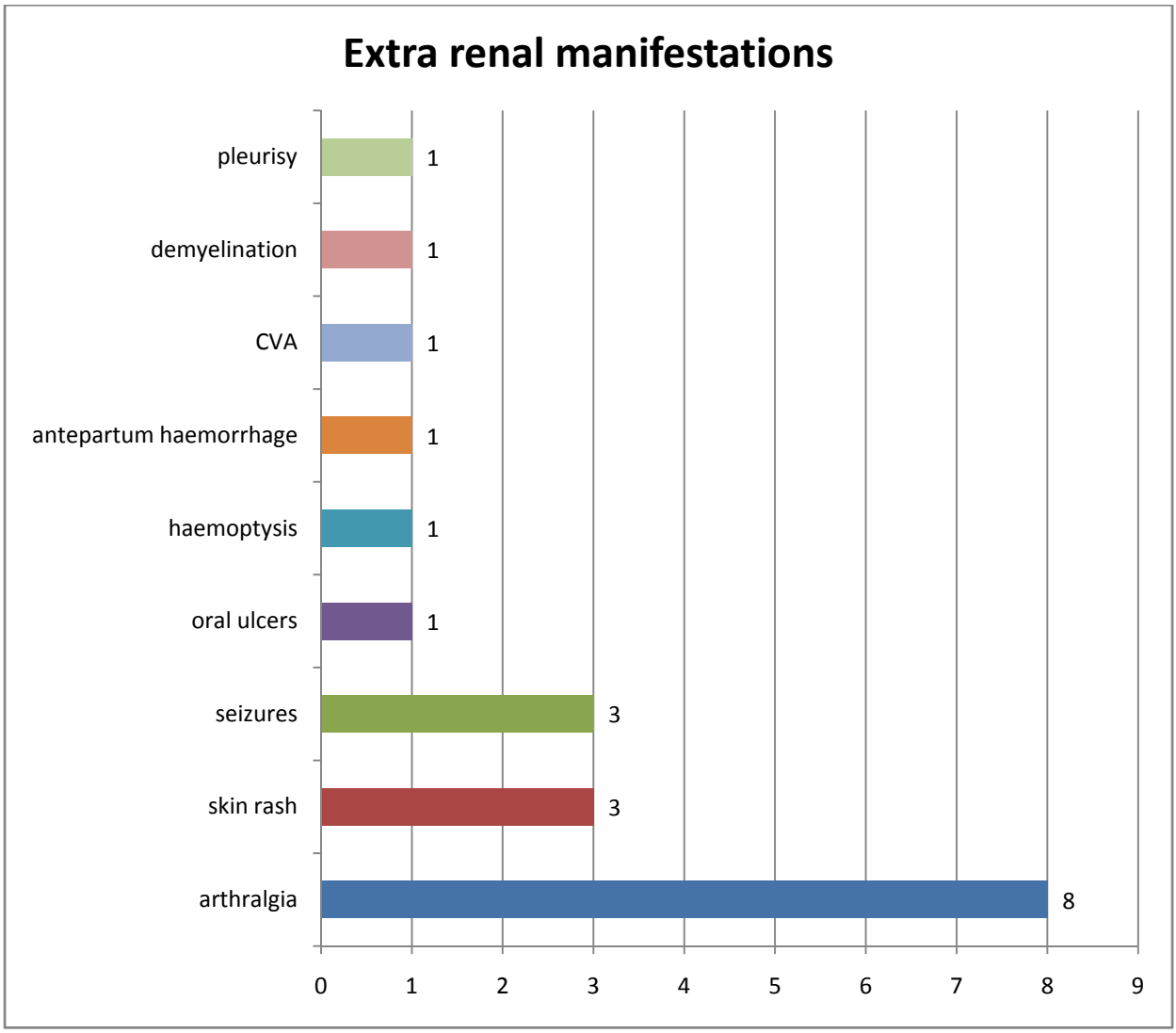


Figure 4: X axis represents the number of patients and the various extra renal manifestations are plotted along the Y axis

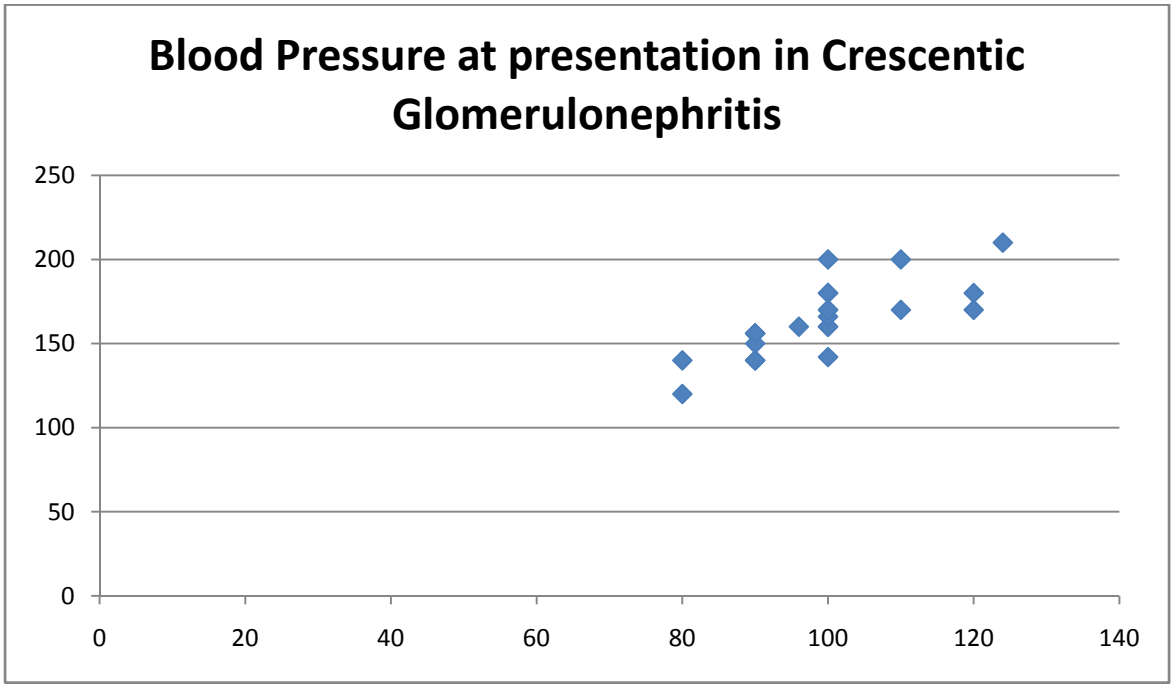


Figure 5: X axis represents diastolic BP in mm Hg; Y axis represents systolic BP in mm Hg. The BP trend of the study population, excluding four patients who were already on antihypertensive drugs at the time of admission is represented as scatter diagram

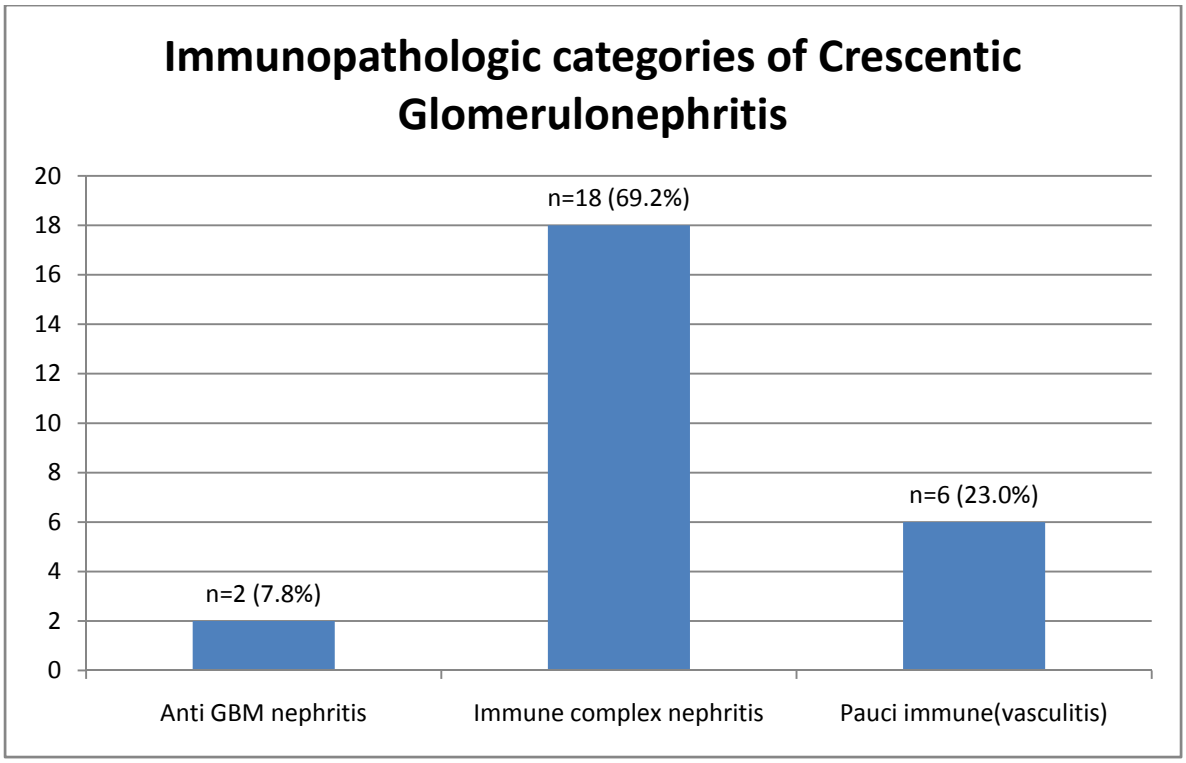


Figure 6: The three pathological categories of Crescentic glomerulonephritis based on immunofluorescence are represented along the X axis; Y axis represents the number of patients.

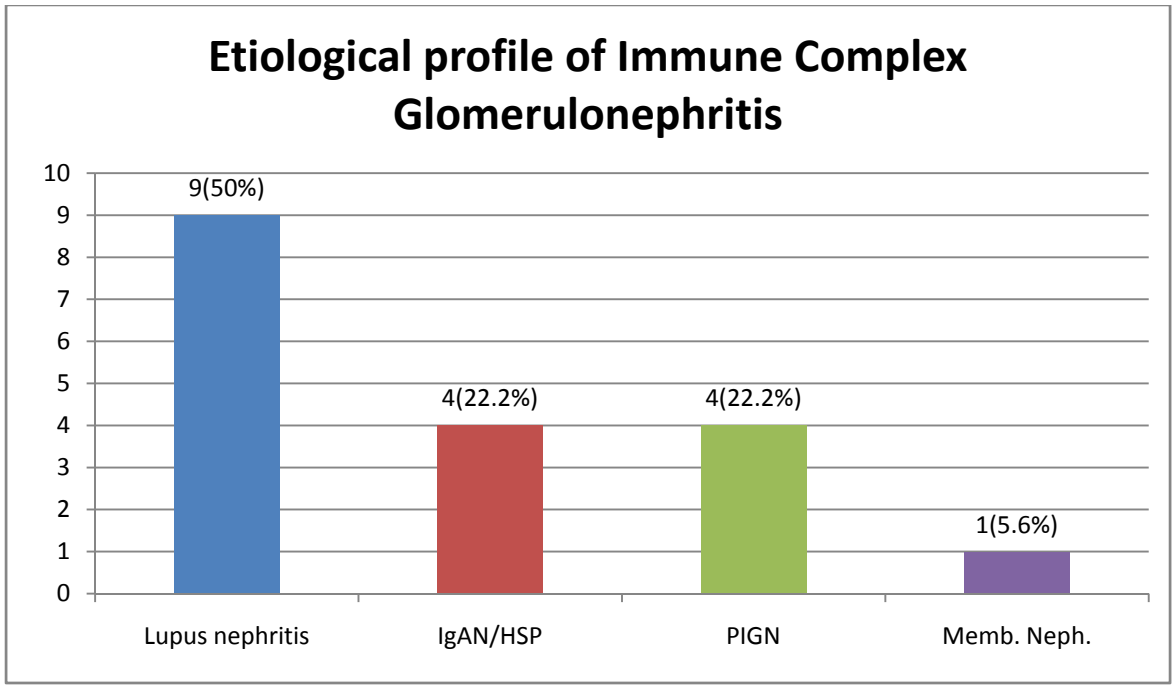


Figure 7: Etiology of Immune Complex Glomerulonephritis based on immunofluorescence & serologic tests. Y axis represents the number of patients. IgAN = IgA Nephropathy; HSP = Henoch Schonlein nephritis: PIGN = Post Infectious Glomerulonephritis; Memb. Neph. = Membranous Nephropathy

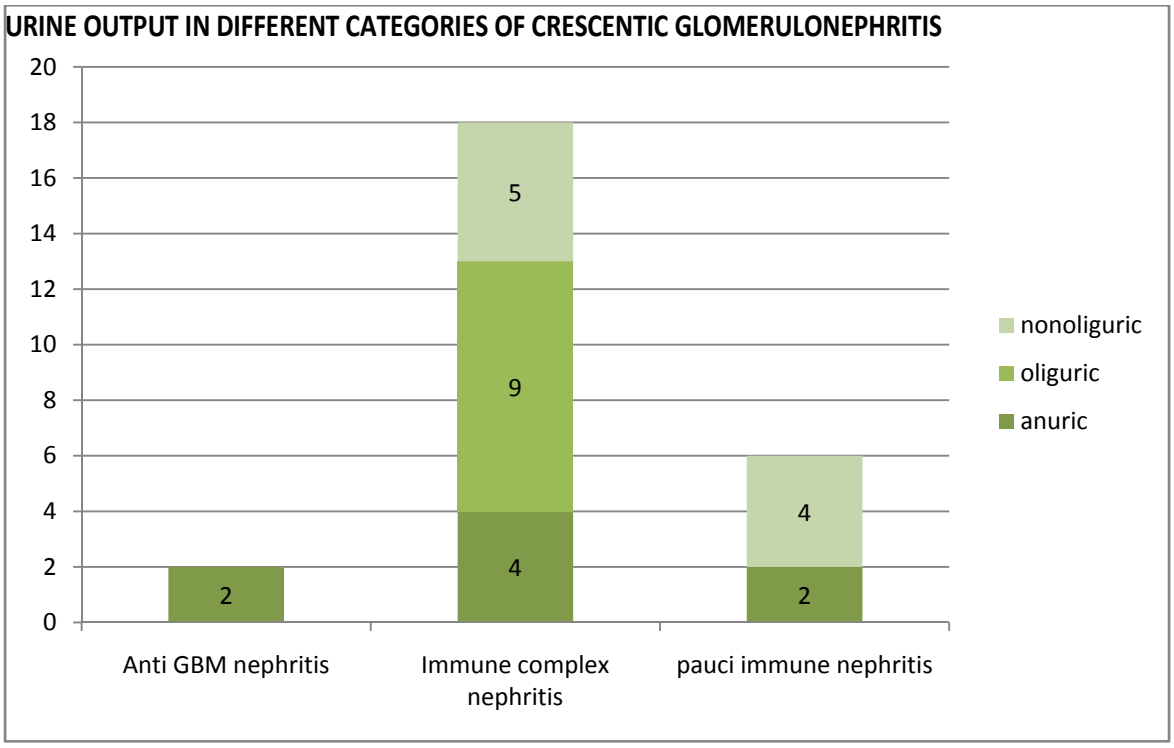


Figure 8: The three types of Crescentic Glomerulonephritis are plotted along the X axis. Y axis represents the number of patients.

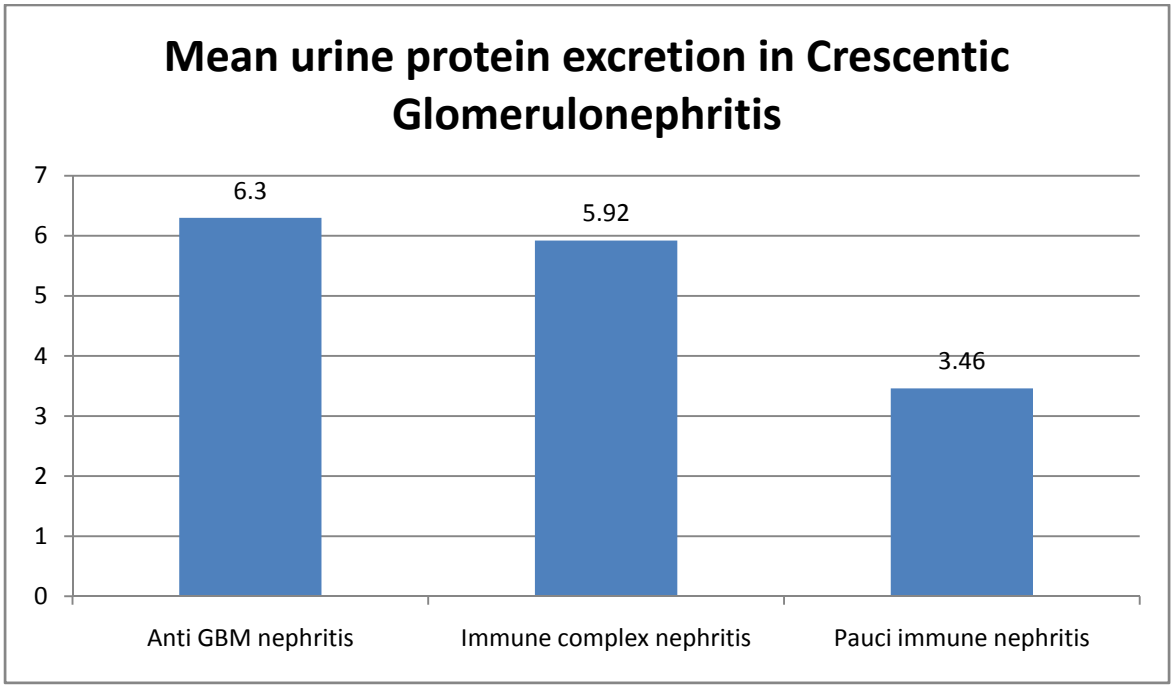


Figure 9: The average spot urine protein creatinine ratio at the time of clinical presentation is represented along Y axis.

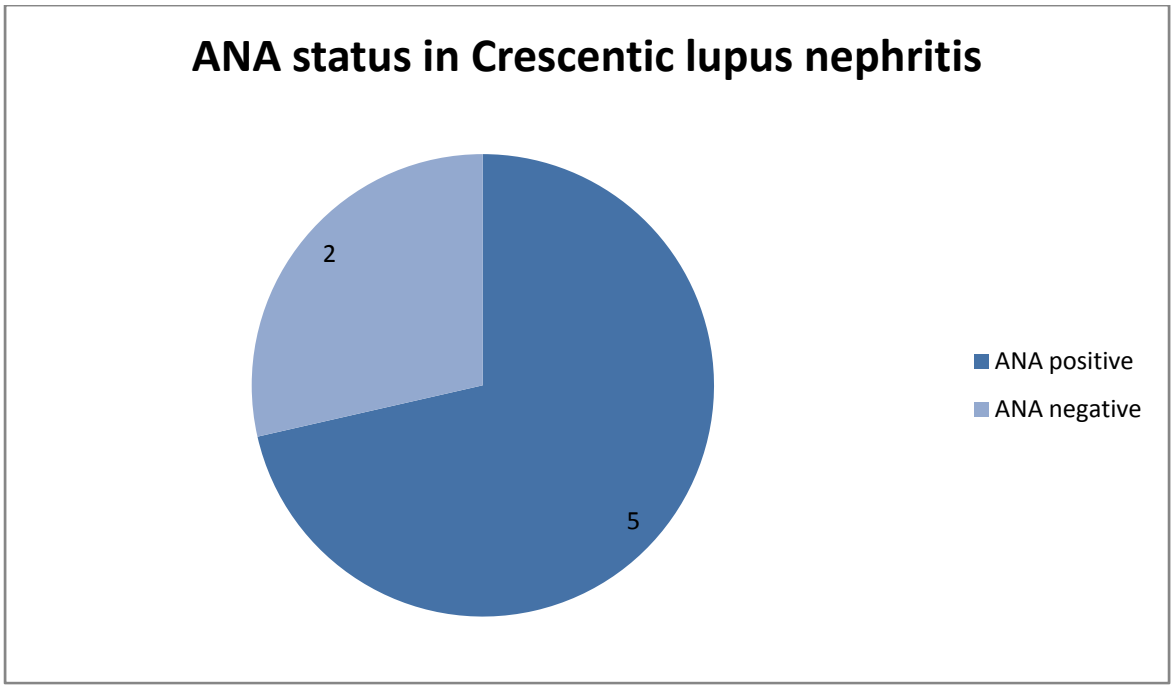


Figure 10: Out of the seven patients with lupus nephritis who were tested for ANA five were found to be ANA positive and two were ANA negative.

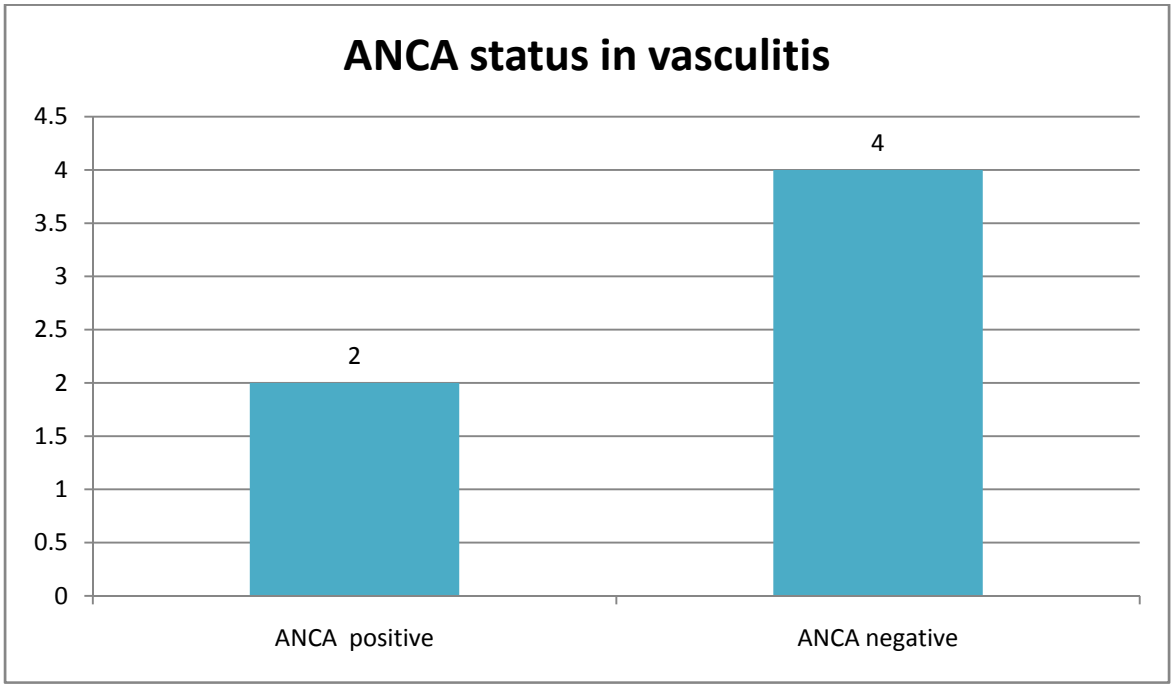


Figure 11: Out of the six patients who had vasculitis, ANCA was positive in two and negative in the remainder. In both only P-ANCA was positive.

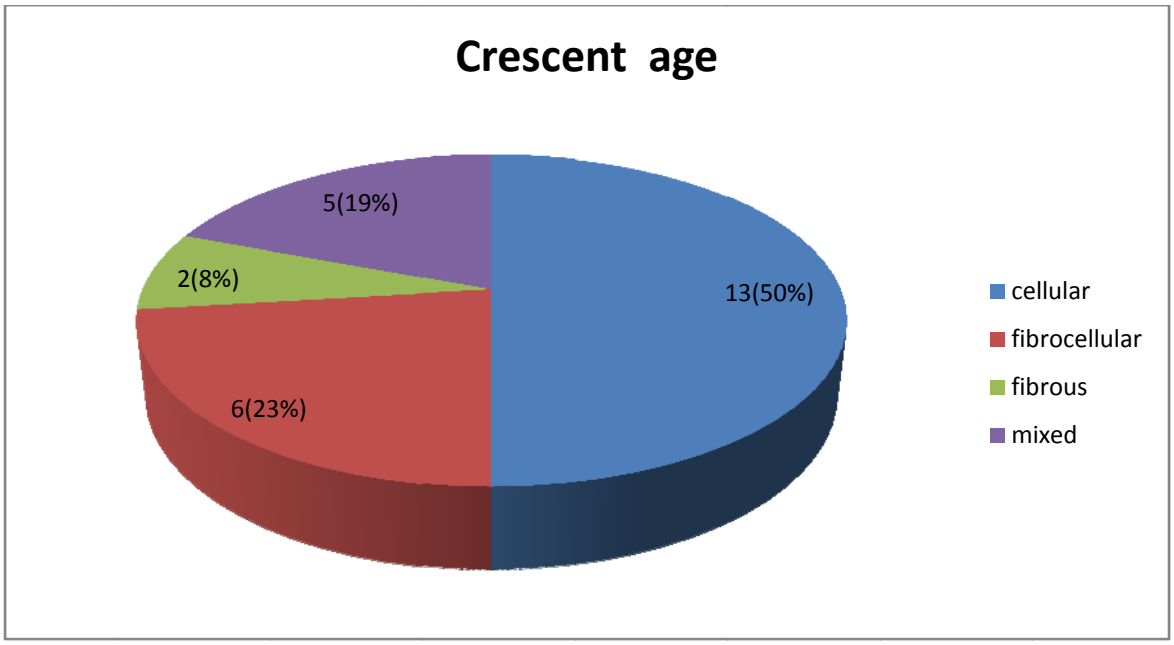


Figure 12: Each sector represents the type of crescent (based on its age) seen in renal biopsy. The number inside each sector represents the number of patients (as % of the total population) showing that particular crescent.

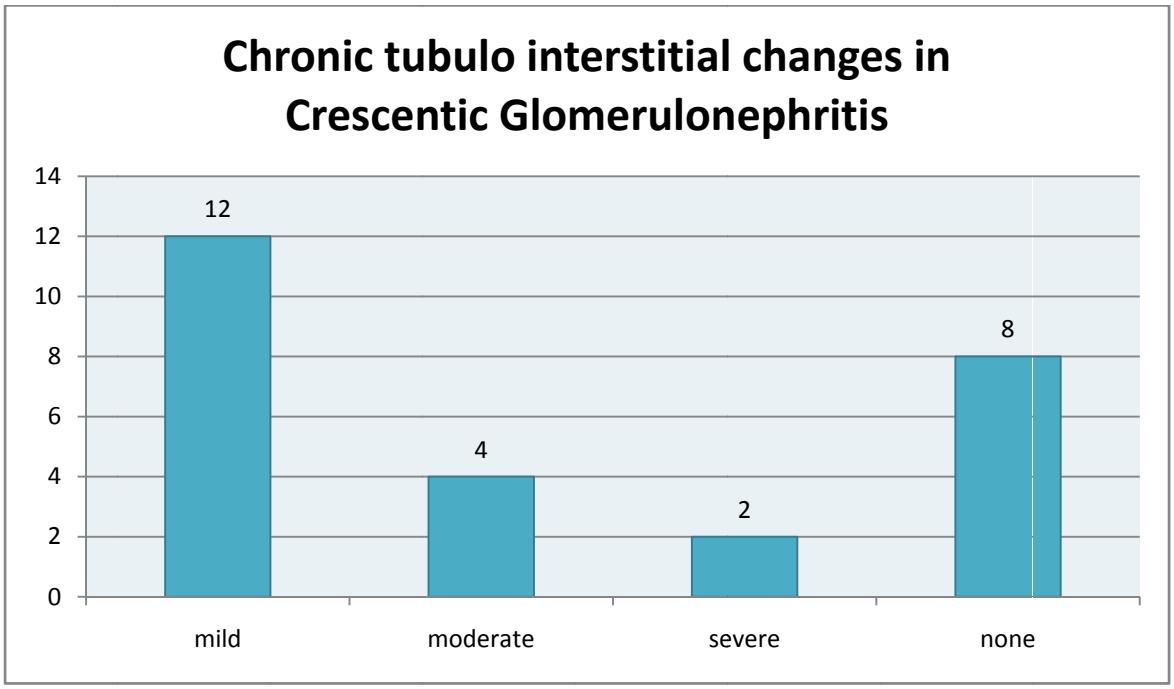


Figure 13: The grades of tubular atrophy and interstitial fibrosis are plotted along the X axis and the number of patients in each category is represented along the Y axis.

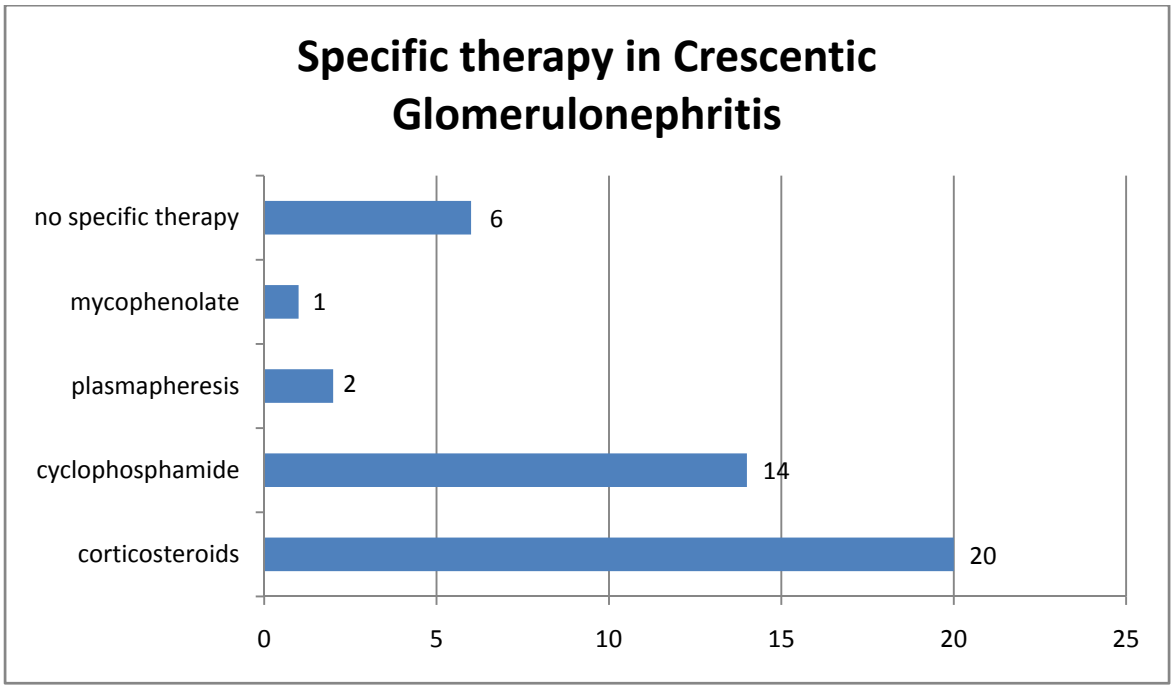


Figure 14: The various specific therapeutic strategies adapted are plotted along the Y axis and the Y axis represents the number of patients treated with a particular strategy.

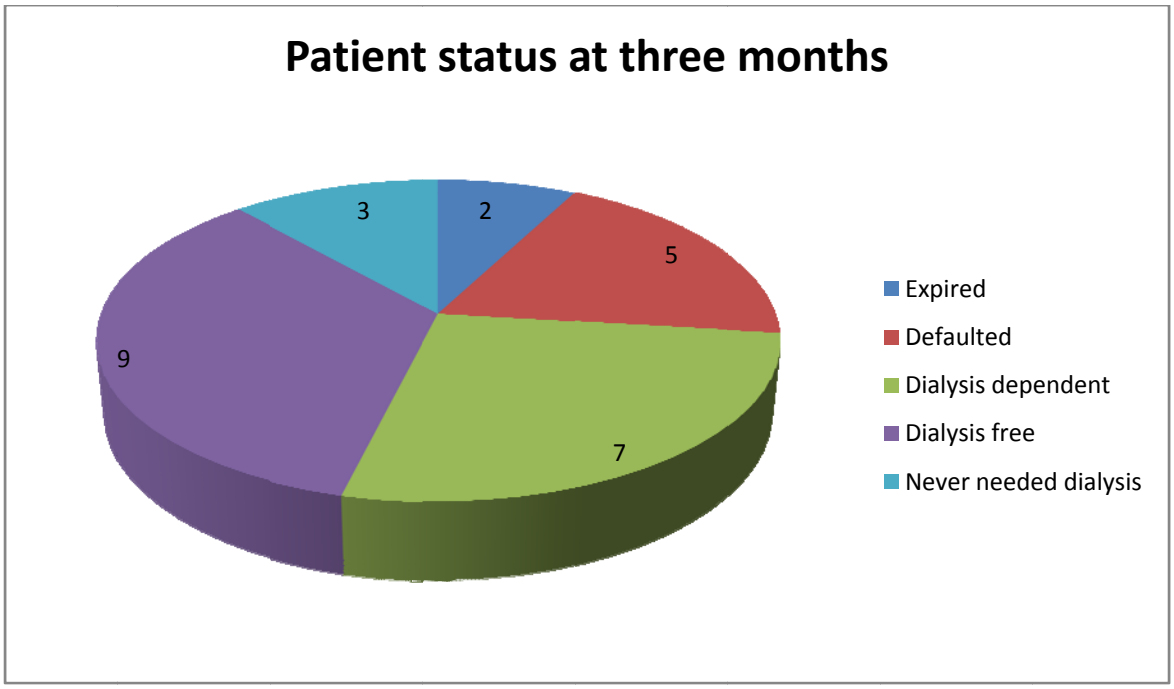


Figure 15: Each sector represents the status of the patient at three months following diagnosis of Crescentic glomerulonephritis.

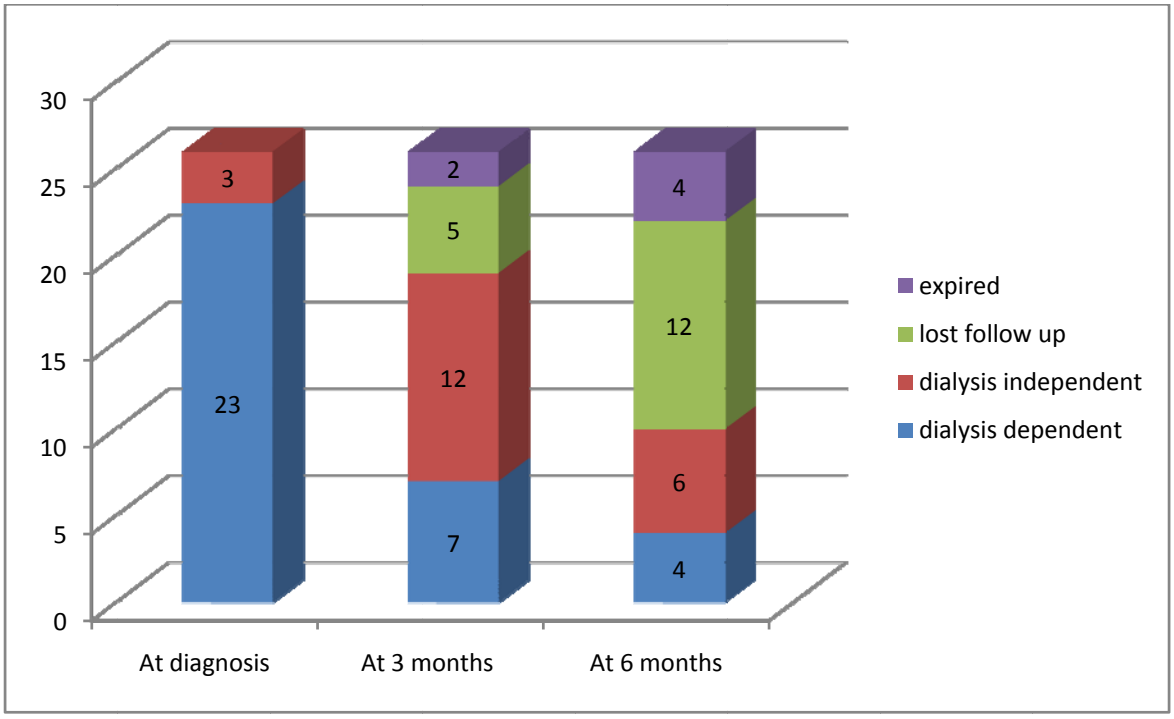
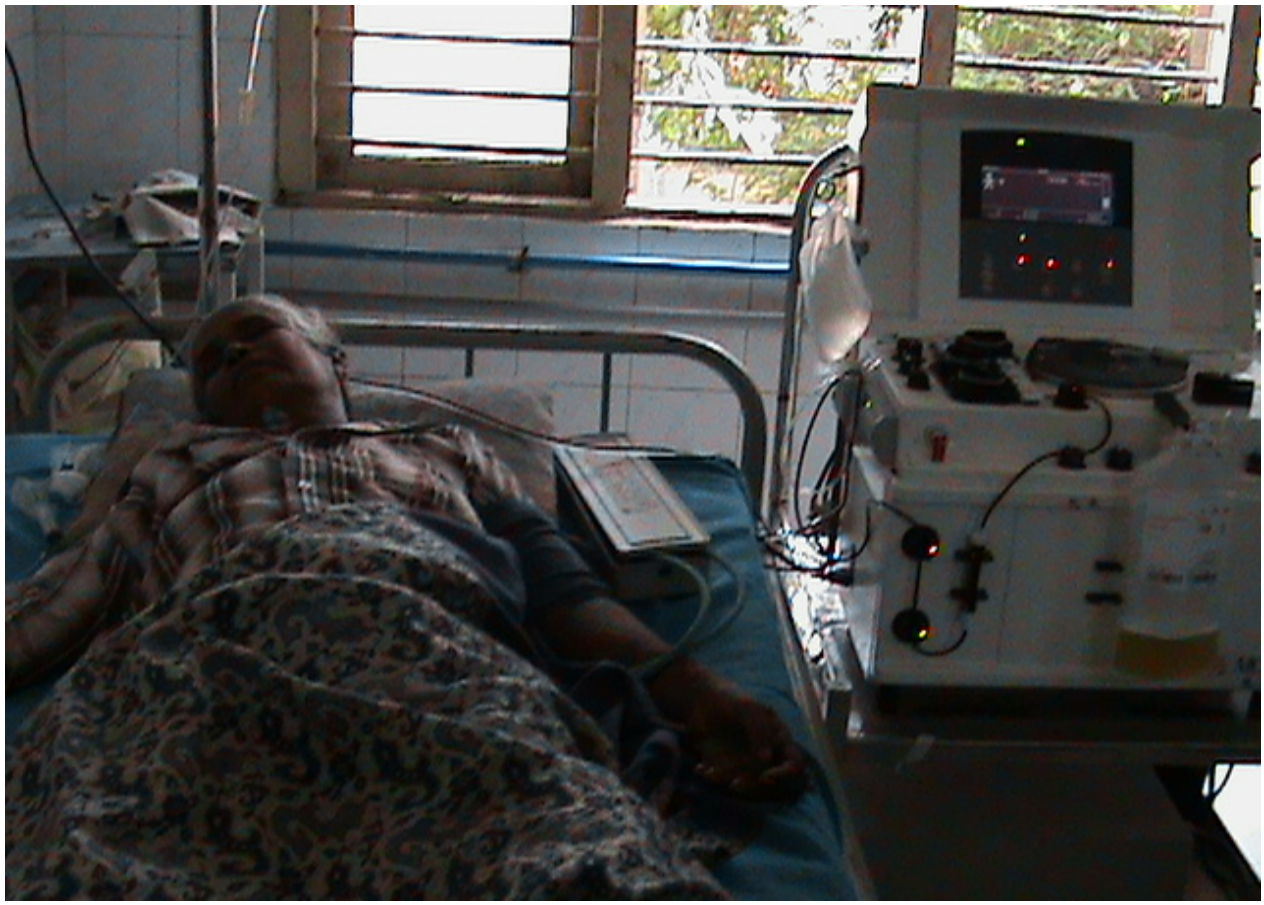
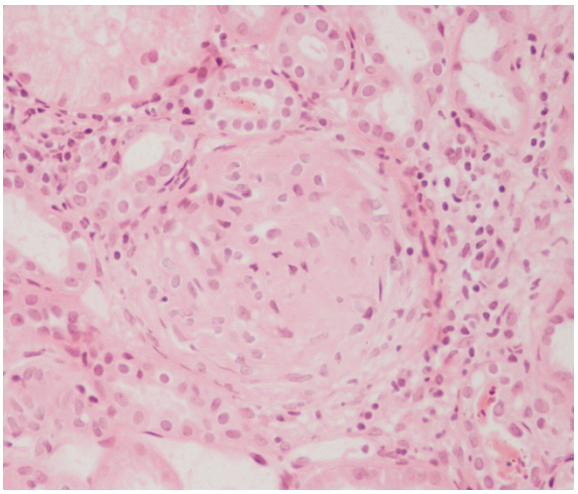


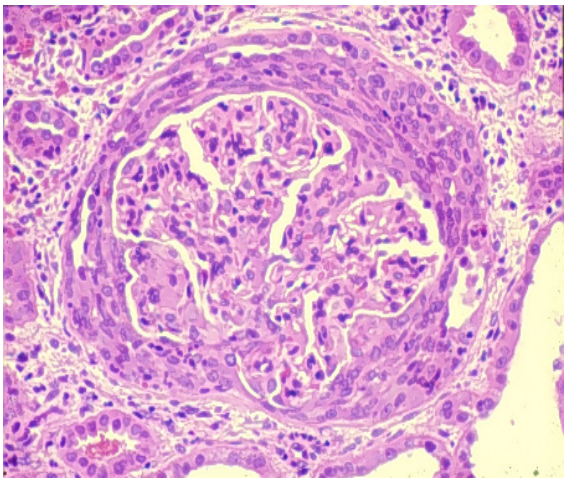
Figure 16: The status of patients at various time periods is shown. X axis represents the time and Y axis represents the number of patients.



Plasmapheresis in progress in a patient (Sl. no 17 In Master Chart) with pauci immune nephritis and severe renal failure



Circumferential fibrous crescent in a patient (sl.no 26)



circumferential cellular crescent in a patient (sl.no 3)