Original Article

PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS: A PROSPECTIVE ANALYSIS

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ABSTRACT

Objective: To assess clinical presentation and outcome of patients with Pauci-Immune Crescentic Glomerulo Nephritis (PICGN) in our setup.

Design: Case series.

Place and Duration of Study: Armed Forces Institute of Urology (AFIU) and Military Hospital (MH) Rawalpindi from November 2007 to October 2009.

Patients and Methods: In a prospective design, patients diagnosed as pauci-immune glomerulo nephritis, were included in this case series. Detailed history along with physical examination and thorough investigation of all cases, including vasculitic screening and renal biopsy were carried out. Disease activity was evaluated with Birmingham Vasculitis Assessment Score (BVAS) and organ involvement assessed by Disease Extent Index (DEI). The patients were treated with a combination of cyclophosphamide and steroids and were followed up on monthly basis. All data was recorded and analyzed using SPSS version 16.

Results: Twelve patients were included in this case series. Beside renal involvement (100%), constitutional symptoms were present in majority of patients (91.7%), lung involvement (58.3%), upper respiratory tract (41.7%) and musculoskeletal system (33.3%). Six patients were positive for c-ANCA and 4 for *p*-ANCA. Three patients (25%) developed End Stage Renal Disease (ESRD). There were five deaths (41. 7%) during study period which included these three with ESRD.

Conclusion: Pauci-immune cresentic glomerulo nephritis is an uncommon systemic disease with varied presentation and has high mortality without treatment. Combined treatment with cyclophosphamide and steroids improves outcome but can have life threatening side-effects. Therefore treatment needs to be individualized and benefit to risk ratio weighed before its commencement.

Keywords: Microscopic Polyangiitis, Pauci-Immune Crescentic Glomerulonephritis, Wegener's Granulomatosis.

INTRODUCTION

Pauci-immune cresentic glomerulo nephritis (PICGN) is a rare disorder presenting as progressive impairment of renal function. This deterioration of renal function may result in chronic kidney disease (CKD) or death especially when patients are dialysis dependent at diagnosis[1-3]. The disease usually begins during the fifth to seventh decade although can occur at any age. There is slight male predominance. In Europe it has a prevalence of 25 per million population[4]. Histopathologically (HP) PICGN appears as variable amount of extracapillary proliferation, fibrinoid necrosis and glomerulosclerosis on renal biopsy with no or minimal deposits on IF microscopy. The majority of patients with PICGN have kidney disease as a part of a systemic small vessel vasculitis including Wegeners granulomatosis and microscopic polyangiitis or as a part of renal limited vasculitis (no other organ involved except kidneys)[5].

Anti-neutrophil cytoplasmic antibody (ANCA) is used as a serologic marker for primary systemic small vessel vasculitis and 80 to 90% of patients with PICGN are ANCA positive[6].

Patients with PICGN are treated with immunosuppressive drugs, which are effective as they increase the survival dramatically and induce complete remission in the majority of these patients[7-9]. However, in approximately 10

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to 15 percent of patients, renal function is inadequately restored, most often in patients who have severe renal dysfunction at presentation[2,3,8,10-12]. In the meantime, these patients are exposed to the potentially lethal adverse effects of these drugs, such as cytopenias thus exposing them to infections[7,14]. The physician has to weigh the chance of recovery of renal functions against adverse effects of these drugs. Extra renal disease manifestations may justify immunosuppressive treatment, irrespective of renal involvement.

In this study we have described our experience with clinical presentation and outcome in our local population with PICGN.

PATIENTS AND METHODS

In this case series, patients presenting with unexplained acute renal failure with normal size kidneys and active urine sediments were admitted and subjected to renal biopsy. Patients with histologically proven focal necrotizing glomerulonephritis and no or little deposits (pauci-imune) on IF were included in the study. All the baseline investigations including urea, creatinine, electrolytes, arterial blood gases, blood complete picture, liver function tests, chest X-ray, paranasal sinus (PNS) X-ray, ultrasound abdomen, electrocardiography, echocardiography and complete vasculitic screen (ANA, RA, ANCA, Anti-GBM, complement C3 and C4 levels) were carried out. Certain investigations including CT scan/MRI brain, HRCT (high resolution CT scan) chest, Bronchoscopy with biopsy and pleural or nasal biopsies were performed in selected symptomatic cases. ENT specialist, ophthalmologist and dermatologist opinion was taken in patients where required.

Testing for ANCA was performed by IF in ethanol fixed neutrophils at initial clinical presentation and was repeated regularly during follow up.

This is an on going case series in which the data was collected on a pre-designed proforma from patients reporting to AFIU and MH Rawalpindi from November 2007 to June 2009. Acute renal insufficiency was defined as an increase of at least 30% of baseline serum creatinine in less than 3 months. Blood-pressure (BP) equal to or less than 140/90 mm Hg was considered normal. The glomerular filtration rate (GFR) was calculated using the Cockcroft – Gault formula. Wegeners granulomatosis, microscopic polyangiitis and renal limited vasculitis were diagnosed according to the Chapel - Hill consensus conference criteria[15]. For classification purposes, chest and PNS X-rays results of all patients were evaluated. Additionally, the results of biopsy of extra-renal organs were considered.

Disease activity at initial clinical presentation was evaluated by using the Birmingham vasculitis assessment score (BVAS)[16]. Vasculitis-related organ involvement was assessed using the disease extent index (DEI)[17].

Paraffin-embedded renal sections were stained with Haematoxylin/Eosin and periodic acid–Schiff. IF microscopy of renal biopsies was carried out in all patients. The IF studies were performed by the classic direct IF using Flourescein Isothiocyanate (FITC) conjugated anti-human IgG, IgA, IgM, complement C3, complement C4 and fibrin antibodies. The tested antisera either did not stain or the staining was scattered. All biopsies were reviewed by the same team of consultant histopathologist / immunologist. Eleven patients had received induction therapy with daily oral or intravenous pulse cyclophosphamide with oral corticosteroids. Intravenous pulse methyprednisolone was administered in majority of patients. Two patients received plasma exchange for extensive pulmonary hemorrhage.

Remission was defined as the stabilization or improvement of renal function and resolution of extrarenal manifestations of systemic vasculitis. The status of complete remission was supported by normalization of laboratory parameters (erythrocyte sedimentation rate, C - reactive protein and leukocyte count). Relapse was defined as a rise in serum creatinine occurring with a nephritic sediment or worsening / new extrarenal

manifestation involving the typical organ systems.

The statistical analyses were carried out using the SPSS-16 package for Windows. Descriptive statistics were performed with standard tests.

RESULT

There were 12 patients in this case series with a recent onset of pauci-immune cresentic glomerulonephritis. They were followed prospectively from November 2007 to June 2009. The mean duration of follow-up was 12.67 months (SD±5.54).

All patients presented with acute renal insufficiency. Seven (58.33%) patients had a serum creatinine of more than 500 µmol/L at presentation and five required hemodialysis at diagnosis. Mean serum creatinine at presentation was 475.75 µmol/l (range 205–916) with a calculated mean GFR of 21.91ml/min (range 44.3 ml/min to 8.7 ml/min). Microhaematuria was present in all cases and nephrotic range proteinuria in two cases. Five (41.7%) patients had hypertension. Constitutional symptoms were present in 11 (91%) patients and included fatigue, night sweats, weight loss and fever. Lungs were affected in 7 (58.3%) cases which presented as hemoptysis, shortness of breath or had lung infilterates on chest radiography. Three (25%) cases had cavitated nodules. Massive pulmonary hemorrhage with respiratory embarrassment occurred in 3 (25%) patients requiring intubation and mechanical ventilation, two of these also received plasma exchange. Upper airway involvement was in five (41.67%) patients and out of these one (8.3%) developed severe otitis media requiring bilateral myringotomies. Broncoscopy with endobronchial biopsies were performed in 5 (41.7%) cases, pleural biopsy in one and nasal biopsy was carried out in two (16.7%) cases. Altogether 6 patients had extrarenal biopsies, in 5 (41.7%) of these there was evidence of vasculitis on histopathology and remaining one was unremarkable.

In disease classification, 8 (66.7%) patients were diagnosed to be suffering from WG and 3 patients from MPA. RLV was present in 1 patient. All patients were tested for ANCA and ten (83.33%) patients had a positive test result. In WG, 6 patients out of 8 (75%) reacted positive for c-ANCA, 1 (12.5%) patient for p-ANCA and 1 patient (12.5%) was ANCA negative. In case of MPA 2 patients out of 3 tested positive for p-ANCA (66.6%) and 1 (33.3%) was ANCA negative. The patient of RLV was p-ANCA positive.

Eleven (91.7%) patients received primary immunosuppressive protocol with daily oral (1.2 to 2 mg/Kg) or intravenous cyclophosphamide (500 to1000mg per m^2 body surface area) with oral corticosteroids (1 to 2 mg/kg). Intravenous pulse methyprednisolone (7 to 15 mg/kg upto a maximum of 1g) was administered in eight patients initially. One patient was treated initially with azathioprine and steroid. Two patients had received plasma exchange for extensive pulmonary hemorrhage. These patients also received prophylactic therapy with trimethoprim-sulfamethoxazole, leuprolide to avoid amenorrhea in young women and hydration to prevent hemorrhagic cystitis. For the toxicities of prolonged glucocorticoid use, prophylactic treatment was given for gastritis (H2 blocker or proton pump inhibitor), and bone loss (calcium, vitamin D and bisphosphonate). After a period of 4 to 6 months, cyclophosphamide was substituted by azathioprine or mycophenolate mofetil.

Three (25%) patients went on to develop ESRD during follow up. Two out of these had more than 50% sclerosed glomeruli with fibrous crescents at presentation and their renal functions did not improve with treatment. One had remission with treatment and had stable renal functions without hemodialysis but unfortunately he stopped his medications and developed ESRD. Relapse in the form of massive hemoptysis secondary to pulmonary vasculitis was seen in three patients. Two of these had poor compliance and were not taking immunosuppressive therapy and in one these medicines were stopped due to recurrent infections. Five (41.7%) patients had died during followup, 3 (25%) patients out of these due to fulminant pulmonary hemorrhage and

the other two died of septic shock. Mean GFR of surviving patients at present is 40.45 ml/min (range 22.8–58.7).

Serum creatinine, BVAS and DEI score at initial presentation significantly correlated with death and final renal function outcome of the patients. Mean creatinine value, BVAS and DEI score of patients who died was 490 umol/L, 7.8 and 27 respectively, in comparison surviving patients had values of 462 umol/L, 6.2 and 20.14 respectively.

DISCUSSION

Pauci-immune cresentic glomerulonephritis is a systemic vasculitis which commonly presents as acute renal failure with active urine sediments and respiratory tract involvement. The principle difference between WG and MPA is the presence of upper respiratory tract involvement and granulomatous inflammation in the former. Patients presenting with only pauci-immune glomerulonephritis in the absence of other organ system involvement are generally classified as renal-limited vasculitis. Because both diseases are highly associated with ANCA, they are sometimes collectively referred to as ANCA-associated vasculitis[18,19].

Published data regarding PICGN is very scarce in Pakistan so this study was undertaken to see the presentation and outcome of PICGN in our population.

Pauci-immune cresentic glomerulonephritis is usually a part of systemic vasculitic disease involving at least one extra-renal organ system, as shown by high DEI score of 6.91. In our study, after renal involvement constitutional symptoms were present in majority of cases (91.7%). The main extra renal organ involvement included lungs (58.3%), URT (50%) and musculoskeletal system (33.3%). Ahmed T et al published a study in 1999 on presenting features in Pakistani patients suffering from ANCA vasculitis, respiratory tract symptoms were present in 82% of cases followed by hematuria in 65% patients[20]. Hoofman et al and Anderson et al published their studies on patients of Wegeners Granulomatosis in 1992[12,21]. These studies, in comparison to our study (Table-2) had

Table-1: Patient demographic, clinical and laboratory characteristics.

Variables	Number / percentage / range
Mean age	44.08 (SD±18.09)
Gender	
Male percent	67%
Extra-renal manifestations	
Constitutional symptoms	91.7%
Musculoskeletal symptoms	33. 3%
Vasculitic skin involvement	16.7%
Lungs involvement	58.3%
Upper resp tract involvement	41.7%
Pericardial effusion	8.3%
Neurological involvement	8.3%
Mean BVAS	23 (15 - 36)
Mean DEI	6.91 (3 - 9)
Disease classification	
Wegener's granulomatosis	66.7%
Microscopic polyangiitis	25%
Renal limited vasculitis	8.3%

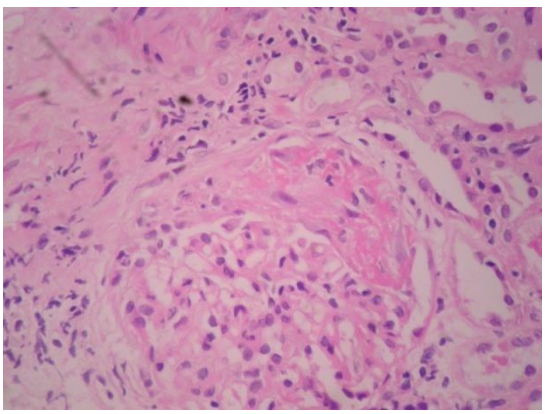

Fig. Renal histology with a crescent, of a patient with PICGN, in our study.

involvement of URT in majority of cases followed by kidneys and lungs. Another study was carried out by Matteson and his colleagues, which was published in 1996[22]. The results of this study are similar to our study (Table 2).

Mortality rate in our patients with PICGN is 42% which is very high. Serum creatinine, BVAS and DEI score at presentation are useful parameters for predicting renal and patient outcome in patients with Pauci-immune glomerulonephritis[23]. Our patients have high serum creatinine, BVAS and DEI score at presentation i.e. 476 umol/L, 23 (range of 15-36)

Table-2: Comparison with other studies.

Organ involvement	Hoofman etal[11]	Anderson et al[20]	Matteson et al[21]	Our study[12]
URT	99	75	NIL	42
Kidneys	70	60	73	100
Lungs	66	63	53	58
Eye	61	14	NIL	17
Heart	25	NIL	14	8
PNS	40	NIL	NIL	NIL
CNS	11	NIL	NIL	8
GI tract	6	NIL	9	NIL
Skin	33	25	NIL	17
Rheumatic	77	20	NIL	33

Figures are given in percentage.
CNS- central nervous system, PNS- peripheral nervous system, URT- upper respiratory tract.

and 6.91 (range of 5-9) respectively. In comparison in Eisenberger et al study cohort, the median serum creatinine was 267.5, median BAVIS of 18.5 (range of 14-29) and median DEI of 5 (range of 4-11)[23]. Higher serum creatinine, BVAS and DEI score at presentation is likely to be due to late referral to nephrologist that has contributed to high mortality rate in our study[24]. In addition poor compliance and infectious complications due to immuno-suppressive medications were the significant determinants.

Cyclophosphamide has revolutionized the treatment of PICGN. Untreated patients have a 90 percent mortality rate within two years. In comparison, some cyclophosphamide studies have reported mortality rates of 20 to 28 percent at five years and 35 percent at 10 years while others have noted even better survival rates (80 percent at 8 years and 88 percent at 12 years)[7,10,25]. Five patients in our study died during follow up, three out of these had massive pulmonary hemorrhage due to pulmonary vasculitis and all these cases were of cyclophosphamide. Two patients on immunosuppressive treatment died due to septic shock. In the surviving patients creatinine clearance had doubled with treatment, from initial mean level of 21.92 ml / min to 40.46 ml/min (92 % increase). Even after development of ESRD, extra renal complications warrant use of immuno-suppressive medications, though a combination of cyclophosphamide and prednisolone in these patients expose them to adverse effects of these drugs[7, 26].

CONCLUSION

Pauci-immune cresentic glomerulone-phritis is a systemic disease with varied presentation. Though uncommon it is a lethal disease and its early recognition and treatment can reduce morbidity and mortality. Treatment with cyclophosphamide and steroids has revolutionized the prognosis from universal mortality to ninety percent survival.

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