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Original Article

Clinical Presentation and Histopathological Profile and Renal Outcome of ANCA Associated Vasculitis

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Abstract
Background: *Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides usually affect various organ systems. Renal involvement usually presents as rapidly progressive renal failure. The clinico-pathological variants are Microscopicpolyangitis, Granulomatosis with polyangitis and renal limited vasculitis.*
Aim: *To study the epidemiological, clinical profile of ANCA associated vasculitis clinico- histo pathological correlation and renal outcome after treatment.*
Materials & Methods: *Retrospective and prospective observational study from June 2015 to May 2018. Patients with active vasculitis, ANCA positive serology and necrotizing/ crescentic pauci immune glomerulonephritis in biopsy were included. Patients aged<13 years, normal urine analysis and normal serum creatinine were excluded.*
Observation & Conclusion: *ANCA associated glomerulonephritis contributed to 2.8% of native kidney biopsies. Common age group was between 51 -60 years. The median age of presentation was 45±10.9 years. Male to female ratio was 1:1.6. 24(61.5%) patients had microspicpolyangitis (MPA), 11 (28%) patients granulomatosis with polyangitis (GPA), four had renal limited vasculitis. Six patients (15%) had ANCA negative vascultis. Joint involvement predicted the renal prognosis of ANCA vasculitis in this study. Sclerotic subtype of ANCA associated vasculitis had poor renal prognosis.*
Keywords: *ANCA, Vasculitis, Renal failure, Renal biopsy.*

Introduction

The Kidneys are highly vascularized organ and are therefore commonly affected by different variants of small vessel vasculitic syndrome. Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides are a group of small vessel vasculitic syndrome affecting various organ systems. The renal involvement usually present as rapidly progressive deterioration of renal function. The renal involvement is an important factor with respect to morbidity and mortality of the patient. The histopathology of renal biopsies shows pauci immune crescentic glomerulonephritis[1].

The frequently occurring clinico-pathological variants of ANCA- associated vasculitis are Microscopic polyangitis, Granulomatosis with polyangitis and renal limited pauci- immune crescentic glomerulonephritis[2]. ANCA associated

glomerulonephritis is characterized by little or no glomerular staining for immunoglobulins or complement. Electron microscopy shows sub endothelial oedema, micro thrombosis and degranulation of neutrophils. Renal involvement is one of the most clinically significant manifestation and most severe form[3,4].

The recent ANCA-glomerulonephritis histological classification has validated in many studies in different ethnicity has diagnostic as well as prognostic value for renal outcome[5]. Despite the difference between PR3- AAV and MPO-AAV, the treatment protocols are the same. Patient survival in AAV has improved substantially over last three decades. Patient survival is worse in MPO- AAV than PR3-AAV but renal survival is equal[6]. More recently the introduction of B cell targeted therapy has been one of the major breakthroughs[7].

Aims & Objectives

1. To study the epidemiological and clinical profile of ANCA associated vasculitis.
2. To study Clinico-histopathological correlation of ANCA associated vasculitis.
3. To study renal outcome after the treatment of ANCA associated vasculitis.

Materials & Methods

Study Design: Retrospective and prospective observational study.

Study Period: June 2015 to May 2018

Study Centre: Department of Nephrology, Kanyakumari Government Medical College, Asaripallam.

Inclusion Criteria

1) Diagnosis of GPA or MPA or its renal limited variant, in accordance with the Chapel Hill consensus conference 2012 criteria with active vasculitis as indicated by the presence of active necrotizing glomerulonephritis on renal biopsy.
2) ANCA Positive Serology
3) Biopsy proven necrotizing/ crescentic pauci immune glomerulonephritis in the absence of another defined glomerulopathy.

Exclusion criteria

1) Patients with age less than 13 years of age.
2) Patients who have normal urine analysis without proteinuria and normal Serum. Creatinine.
3) Unwillingness for biopsy.

Demographic data like age, sex, BMI, presence of co-morbid illness like diabetes mellitus, hypertension, seizure disorder and asthma were noted in detail. Clinical presentation of symptoms and signs like edema, oliguria, haematuria and haemoptysis were documented. Detailed clinical examination including blood pressure measurement and complete clinical examination including ENT and Ophthalmology was done. Blood pressure more than 140/90mmHg was considered hypertension.

Renal biopsy

Renal biopsy was performed in all patients presented with rapidly progressive renal failure, pulmonary renal syndrome and unexplained renal failure. Renal biopsy was done in prone position using ultrasound locating the lower pole of kidney under aseptic precaution with local anaesthesia with biopsy gun. Core biopsy specimen was sent for light microscopy (in formalin) and immunofluorescence (in Michel's fixative).

In light microscopy haematoxylin and eosin, Periodic acid –Schiff, Jone's Methenamine silver stain and Masson's trichrome staining were used. In Immunofluorescence, all the routine immunoglobulin IgG, IgA, IgM light chain λ and k and complement C3, C1q panel were done. A minimum of 10 glomeruli was considered adequate to classify the specimen.

The standardized definition by Berden *et al*, glomerular lesions[1] were followed

1) Normal glomeruli referred to glomeruli without vasculitic lesions or global sclerosis.

2) Global glomerulosclerosis referred to sclerotic changes in the glomerular tuft for 80%
3) Cellular crescents referred to cellular components of the crescent for 20% or more.
4) Fibrous crescents referred to extracellular matrix of the crescent for 90%.
5) Focal lesions defined as the presence of ≥50% normal glomeruli.
6) Crescentic category was defined as presence of ≥50% cellular crescent.
7) Mixed category involves combination of both normal, crescentic and sclerotic glomerulus <50%
8) Sclerotic category included biopsies of ≥50% globally sclerotic.
9) Interstitial and tubular lesions were scored semi quantitatively.

Treatment

Treatment protocol consists of induction therapy followed by maintenance therapy for 18 months.

Induction therapy: The induction therapy included IV methyl prednisolone 500 mg IV for 3 days followed by oral prednisolone1mg/kg/day for 4 – 6 wks then tapered over 3 months then maintainedat 10 – 15 mg/d for next 1 year in combination with cyclophosphamide IV pulse therapy of 500mg infusion (15 mg/kg) every two weeks for 3 doses then every 3 weeks for 7 doses. Cyclophosphamide dose was adjusted depending upon creatinine clearance and body weight.

In double positive patients (ANCA and anti GBM antibody) or dialysis dependency (serum creatinine >5.8 mg/dl), or pulmonary alveolar haemorrhage plasmapheresis was performed in the dose of 30ml/kg/session for 5-7 sessions over 10 days. At 3 months patient were re-assessed. If no remission/dialysis dependency IV cyclophosphamide was stopped and switched over to azathioprine and oral prednisolone. For maintenance therapy, azathioprine 2mg/kg/d with oral prednisolone 10mg/d was given for 18 months.

Renal Outcome Assessment Following Therapy

Renal response to therapy analysed by the end of 3rd month, 6th month and 1 year by

1) Complete recovery of renal function was indicated by normalization of renal function and resolution of hematuria.
2) Partial recovery of renal function(50% reduction of initial value of serum creatinine)
3) Treatment failure– ESKD – on HD/CAPD.

Mean Follow up Period: 18 months

Observation & Results

Statistical analysis: Analysis was performed with the SPSS (Version 22.0, Chicago, IL) statistical software package. Descriptive statistics like mean, standard deviation and proportions were calculated. To compare the proportions Chi – square test, Fisher exact test, one way analysis of variance was performed. Multivariate analysis by cox regression model and Kaplan – Meier survival analysis were used to assess renal and patient survival. In analytic procedure a *p* – value of <0.05 was considered significance.

Demographic and Clinical data

There were thirty nine patients with new diagnosis of ANCA – associated glomerulonephritis accounting for 2.8% of native kidney biopsies performed form January 2012 to December 2015. Among 39 patients, 15(38.5%) were male and 24(61.5%) were female, with a M:F ratio of 1:1.6.Average age of patients 45 ±10.9 years (range 23 -65 years) at time of renal biopsy.

According to the Chapel Hill Consensus 2012 definitions, 24(61.5%) patients were classified as Microscopic polyangitis (MP),11 (28.2%) as Granulomatosis with polyangitis (GPA), and 4(10.3%) as Renal limited vasculitis(RLV). MPA was more common in female (7 male and 17 female ratio of 1:2.4) and a slight male preponderance was found in GPA (6 male and 5 female ratio 1.2:1). Twenty seven of 39(69.2%) patients were positive for perinuclear ANCA(p ANCA). Seven of 39(17.9%) patients were

positive for cytoplasmic ANCA (c ANCA). Five of 39(12.8%) were negative for ANCA. or ANCA was tested by indirect immunofluorescence test method.

Table 1 Demographic data

	TOTAL(39)	MALE(15)	FEMALE(24)
MPA n(%)	24(61.53)	7(46.7)	17(70.8)
GPA n(%)	11(28.20)	6((40)	5(20.8)
RLV n(%)	4(10.25)	2(13.3)	2(8.3)

Table 2 ANCA (IIF) Test in association with AAV variants

	cANCA (n= 7)	pANCA (n=27)	ANCA Neg (n=5)
MPA	-	21	3
GPA	7	3	2
RLV	-	3	1

Table 3 Clinical in ANCA – subgroups characteristics of 39 patients

	MPA (n=24)	GPA (n=11)	RLV (n=4)
Fever n (%)	15(62.5)	6(54)	-
Oliguria n(%)	19(79)	8(72)	3(75)
Haematuria n(%)	11(45.8)	4(36)	4(100)
Edema n(%)	12(50)	6(54.5)	-
Joint involvement n(%)	18(75)	3(27.2)	-
Skin involvement n(%)	17(70.8)	4(36)	-
Haemoptysisn(%)	6(25)	3(27.2)	-
Neurological Weakness n(%)	3(12.5)	1(9.1)	-
Hypertensionn (%)	12(50)	4(36)	1(25)

Table – 4 Lab –parameters in ANCA associated vasculitis subgroups

	MPA (n= 24)	**GPA (n= 11)**	**RLV (n= 4)**
Hemoglobin (g/dl)	7.73±1.5	8.0±1.5	9.28±1.5
Creatinine (mg/dl)	7.8±3.7	6.7±3.7	6.4±3.7
U.PCR	5.5±2.4	4.1±2.4	4.8±2.4
BVAS(v3)	18.1±5	18.2±5	11±5

Table - 5 Histological category with Renal survival and patient survival analysis

Histology versus renal survival								
			Outcome end				**Total**	**P value**
			CKD	**Death**	**ESRD**	**NRF**		
Histological Category	**Cresent**	Count	3	5	8	3	19	0.128 Fishers exact test (Not significant)
		% within histo	15.8%	26.3%	42.1%	15.8%	100.0%	
	Focal	Count	2	0	2	3	7	
		% within histo	28.6%	0.0%	28.6%	42.9%	100.0%	
	Mixed	Count	0	1	4	0	5	
		% within histo	0.0%	20.0%	80.0%	0.0%	100.0%	
	Sclerotic	Count	1	0	7	0	8	
		% within histo	12.5%	0.0%	87.5%	0.0%	100.0%	
Total		Count	6	6	21	6	39	
		% within histo	15.4%	15.4%	53.8%	15.4%	100.0%	

CKD- Chronic kidney disease; ESRD – End stage renal disease; NRF- Normal renal function. Histological classification of ANCA associated glomerulonephritis. Correlating with the renal survival there is ascending order of risk and p- value of 0.128 which is statistically significant.

Table - 6 Distribution of glomerular and tubulo interstitial lesions in AAV subgroups

	MPA, n=24	GPA, n=11	RLV, n=4
Normal glomeruli n (%)	11(46)	5(45)	3(75)
Crescent n (%)	23(95)	9(81)	4(100)
Fibrinoid necrosis n (%)	10(41)	7(63)	2(50)
Glomerulosclerosis n (%)	19(79)	9(81)	1(25)
Vascular – Fibrointimal proliferation n (%)	6(25)	1(9)	-
Interstitial infiltrate n (%)	19(79)	10(90)	3(75)
Interstitial granuloma n (%)	-	2(18)	-
Acute tubular injury n (%)	7(29)	2(18)	-
IFTA (≥25%) n (%)	5(20)	2(18)	1(25)
Linear IgG + n (%)	8(33)	1(9)	1(25)
C3 deposit n (%)	6(25)	2(18)	1(25)

Table 7: Histological categories in ANCA subgroups

	Focal	Crescentic	Sclerotic	Mixed
MPA	4(16)	13(55)	3(13)	4(16)
GPA	3(28)	2(18)	5(45)	1(9)
RLV	-	4(100)	-	-

Table 8 Comparison of BVAS score and laboratory parameters of four histological categories

	Focal (n=7)	Crescentic (n=19)	Sclerotic (n=8)	Mixed (n=5)
Creatinine	4.2±3.7	8.4±3.7	7.1±3.7	8.3±3.7
Urine PCR	4.5±2.4	4.9±2.4	6.7±2.4	4.6±2,4
BVAS	19.2±5	16.4±5	17.9±5	18±5

Treatment outcome of the four histological classifications

	Focal (n=7)	Crescentic (n=19)	Sclerotic (n=8)	Mixed (n=5)
Dialysis Independency Sr.Cr<1.6 mg/dl	3(43%)	3(16%)	-	-
Dialysis Independency Sr.Cr>1.6 mg/dl	2(28.5%)	3(16%)	1(12%)	-
ESRD	2(28.5%)	8(42%)	7(88%)	4(80%)
Death	-	5(26%)	-	1(20%)

Discussion

ANCA associated vasculitis is commonly presented as rapidly progressive GN and renal biopsy shows necrotizing pauci immune GN. Renal biopsy is the gold standard method to diagnose and has a prognostic significance. The serological testing of ANCA by indirect immunofluorescence technique, pANCA, cANCA along with specific clinical features, characteristic organ involvement usually clue to the diagnosis of GPA, MPA.

ANCA associated vasculitis with renal involvement is a severe form of disease with indication for starting immunosuppressive drugs for prolonged course. It is associated with high risk of infections, co-morbid illness and disease activity itself leads to fatal outcome. Recent histological classification of ANCA- associated glomerulonephritis could be useful for prognostic value at the time of biopsy.

In our study, we included 39 patients with renal biopsy proven ANCA– associated pauci – immune glomerulonephritis. It contributed for 2.8% of total native kidney disease. The proportion of male and female in the ratio 1:1.6, 15 were male and 24 were female with mean age of 45±10.9 (range 23 – 65) years at the time of biopsy.

ANCA associated glomerulonephritis contributed to 2.8% of total native kidney biopsies performed between June 2015 to May 2018. The most common age group was between 51 -60 years.

The median age of presentation was 45±10.9 years. Male to female ratio was 1:1.6 (female predilection). Fever (54%), joint involvement (54%), oliguria (69%) and skin involvement 21(54%) are the most common clinical features in ANCA – associated vasculitis. pANCA was present in most MPA (87.5%)patients and all cANCA was positive in all GPA (100%) patients. ANCA test (IIF) was negative insix patients (15%), Anti GBM antibody was positive in 8 patients (20%).

Among 39 patients, 24(61.5%) were diagnosed as microscopic polyangitis (MPA), 11 patients (28%) were diagnosed as granulomatosis with polyangitis (GPA), 4 patients (10.5%) were diagnosed as renal limited vasculitis (RLV).

Crescent (93%), fibrinoid necrosis (49%), interstitial mononuclear infiltrate (82%),interstitial granuloma(5%) and fibrointimal proliferation in arterioles(18%) were noted. Histological category of ANCA associated glomerulonephritis had poor prognostic significance in the renal outcome in the ascending order of focal, cresentic, mixed, and sclerotic category at the time of biopsy. Among clinical features, joint involvement (54%), hypertension at presentation (46%), serum creatinine at presentation (7.3 mg/dl), BVAS score (18) had significant renal prognostic value. Mortality occurred in 6 (15%) patients.

Twenty one patients (54%) progressed to dialysis dependency within 3 months.

Six patients (15%) had good renal function at 18 months follow up after treatment.

Six patients (15%) had progression to chronic kidney disease but remained dialysis independent at 18 months follow up.

Limitations

1. Number of patients included in the study was less.
2. ANCA test was done by indirect immunofluorescence method only.

Conclusion

ANCA associated glomerulonephritis contributed to 2.8% of total native kidney biopsies. The median age of presentation was 45±10.9 years at the time of presentation. Male to Female ratio was 1:1.6 (female predilection.)

Fever (54%), joint involvement (54%), oliguria (69%) and skin involvement are the most common clinical feature in ANCA associated glomerulonephritis. Among 39 patients, 24(61.5%) had microscopic polyangitis (MPA), 11 (28%) patients had granulomatosis with polyangitis (GPA),4 patients had renal limited vasculitis.

Six patients (15%) had ANCA negative vasculitis. Among clinical features, joint involvement (54%), hypertension at presentation (46%), serum creatinine at presentation (7.3 mg/dl), BVAS score (18) had significant renal prognostic value .

The histological category of ANCA associated glomerulonephritis had prognostic significance in the renal outcome in the ascending order of poor prognosis with focal, crescentic, mixed and sclerotic category at the time of biopsies. Prognosis of ANCA associated GN was poor -27 patients (69%) had progressed to chronic kidney disease (21 patients on dialysis dependent and 6(16%) had dialysis independent.

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