Pulmonary-Renal Syndrome in Patients with ANCA (+) vasculitis: An Eleven-Year Single Center Experience

Stangou M, Asimaki A, Zoumbaridis N, Bamichas G, Christidou F, Natse T, Galanis N, Christaki P, Patakas D, Sombolos K
Renal Unit, G. H «G. Papanikolaou», Thessaloniki

Introduction

Small vessel vasculitis and particularly Wegener's granulomatosis, microscopic polyangiitis and Churg Strauss syndrome, can cause pulmonary-renal syndrome[1]. They are also frequently, up to 90%, associated with the presence of antineutrophil cytoplasmic antibodies (ANCA)[2,3] in the serum. So, these vasculities can also be divided into two major categories, those associated with antibodies against myeloperoxidase [MPO-ANCA (+)] and those against proteinase 3 [PR3-ANCA (+)][4,5].

Respiratory involvement usually presents with hemoptysis or acute respiratory failure needed ventilatory support [6,7], although some times a more indolent initiation of the disease can expressed.

The aim of the present study was to report the clinical course and outcome in a series of patients with PRS and ANCA positive vasculitis.

Patients and Methods

We retrospectively analyzed the records of 22 patients with pulmonary-renal syndrome and ANCA (+) vasculitis who were hospitalized from 1992 to 2002 in our Hospital. Renal biopsy was performed in all of them. Renal function was evaluated at time of presentation, one month after the initiation of the treatment and at the end of follow up period. All patients received cyclophosphamide given initially IV, 3 boluses of 0.5-1 g every 10-15 days and continued orally 1-2 mg/Kg/d, for a total period of 3-4 months. Steroids were also given IV in the beginning, Solu Medrol 7-15 mg/Kg/d for 3-4 days and continued as methyprednisolone 48 mg/d per os divided in 3 doses. Three to four months later, Azathioprine or Mycophenolate Mofetil (the last 4 years) was substituted for cyclophosphamide.

Plasma exchange was performed daily (3L exchanges, for 7-14 days) only in patients who were dialysis depended and/or had severe hemoptysis at presentation. All values are expressed as mean ± SD. Statistical analysis included paired and unpaired student's t-test as well as chi-square test.

Results

Patient characteristics at presentation

All patients presented with symptoms from the lower respiratory track, while renal involvement was discovered during their hospitalization. Twenty out of the 22 patients (91%) had impaired renal function (serum creatinine ≥ 1.5mg/dl) and 8/22 (36%) required dialysis treatment on admission. Mean serum creatinine (Scr) levels were 6.6±4.4mg/dl and mean proteinuria 1.6±1.4g/24hr, while only one patient (4.5%) had nephrotic syndrome at presentation.

All patients had positive ANCA, 9 PR3 (+) and 13 MPO (+).

Treatment and course

During the 1st month of treatment, Scr reduced in 12/22 (54.5%) patients (group A), from 8.5±4.5 mg/dl to 4.3±2.3 mg/dl, p=0.001 and increased in 9/22 (41%) patients (group B), from 4.1±3 mg/dl to 6.5±2.9 mg/dl, p=0.03. One patient (4.5%) died from sepsis.

At the end of the follow up period, (4.4±3.3 years), serum Scr reduced further in patients of group A, to 3.8±3.2 mg/dl and deteriorated in patients of group B to 6.7±3.1 mg/d (Fig 1). The difference of final Scr between the two groups was significantly different, p=0.04.

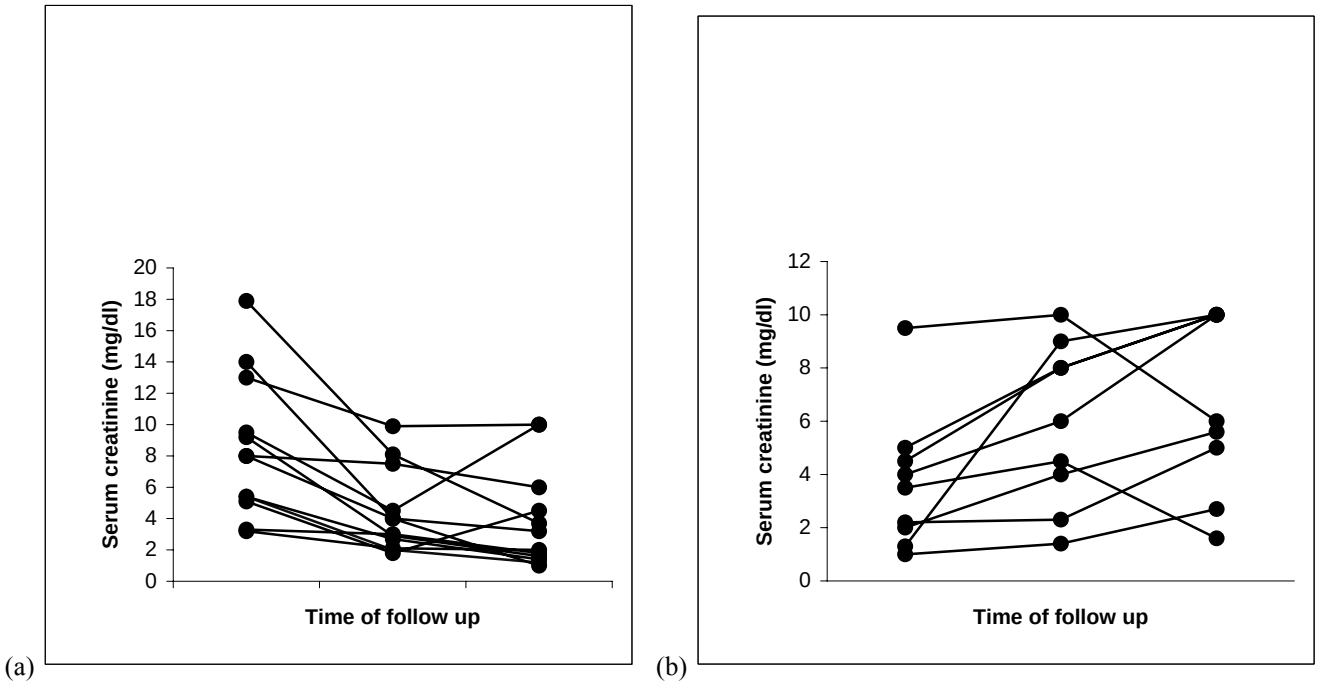
The only significant difference between patients in groups A and B were the initial Scr levels, 8.5±4.5mg/dl in group A and 4.1±3mg/dl in group B, p=0.03.

Group A

After the first month of treatment, and till the end of follow up, renal function improved in 10/12 patients and deteriorated only in two of them, who reached end stage renal disease. Five of the 12 patients (42%) finally died, four (4) from respiratory failure. Among the 5 patients who died, 4 had improved renal function and one was on hemodialysis. So, at the end of the study period, 6/12 (50%) patients had improved renal function, 1/12 (8%) was on hemodialysis and 5/12 (42%) had died.

Correspondence to: Kostas Sombolos, Vas. Olgas 82, Thessaloniki 54643, Greece, fax +30 2310 358481
e-mail: sobolos@spark.net.gr

Fig. 1: Renal function outcome in patients who had initially (a) improved and (b) stable or deteriorated renal function.



(a) (b)

Group B

Renal function gradually improved in 2/9 (22%) patients and deteriorated in 7/9 (78%) while 4/9 (44%) reached ESRD. Five of the 9 patients (56%) finally died, four (4) from respiratory failure. Among the 5 patients who died, two were on hemodialysis, one had renal function deterioration and two had renal function improvement. So, at the end of the study 2/9 (22%) remained with deteriorated renal function, 2/9 (22%) had reached ESRD and 5/9 (56%) had died.

The outcome of renal function differed significantly between the two groups of patients. During the follow up period, preservation of satisfactory renal function was observed in 10/12 patients in group A, compared to 2/9 in group B, p=0.005. Interestingly, however, there were not significant differences in the mortality rate, between the two groups.

Clinical and laboratory differences between PR3 and MPO-ANCA (+) patients are listed in table 1.

Discussion

In the present series we tried to analyze the clinical course and outcome of patients with PRS and ANCA positive vasculitis. The frequency of pulmonary involvement has been estimated to 56% in PR3-ANCA (+) patients and 33% in MPO-ANCA (+) patients[4,6].

Pulmonary manifestations in our study varied widely, from mild dyspnea and fatigue to massive hemorrhage and acute respiratory failure. 13.6% of patients [all PR3-ANCA (+)] presented with respiratory failure, needed urgent ventilatory support. The need for mechanical ventilation in other series has been estimated up to 11% of patients with ANCA associated pulmonary disease[6].

Some investigators believe that pulmonary disease takes a more aggressive course in PR3-ANCA patients[8-10], although this hasn't been confirmed by others[11]. Pulmonary interstitial fibrosis was present in two of the 9 MPO-ANCA (+) patients and in one of them it was known one year prior to diagnosis of vasculitis. Chest CT has been proved valuable in the diagnosis of interstitial fibrosis[12].

There are rare cases, in the literature, of MPO-ANCA (+) vasculitis developed in patients with pre-existing pulmonary fibrosis[13-16]. Patients usually present with respiratory failure, without pulmonary hemorrhage and prognosis is usually poor.

It is generally accepted that respiratory involvement in vasculitis is a factor of increased mortality, estimated to 30-57% during the first year and reaching 60% in patients with acute respiratory failure[17,18]. In our study the mortality rate was 4.5% in the first month after diagnosis, 32% during the first six months, and 50% at the end of follow up. Respiratory failure was responsible for the 73% of deaths occurred till the end of follow up. During the acute phase of disease, patients died because of respiratory failure, due to pulmonary vasculitis. In the later stages, deaths were due mainly to treatment complications. Interestingly, there were no differences in the mortality rate between patients who showed initially improved or deteriorated renal function.

Regarding the differences between PR3 and MPO-ANCA vasculitits, PR3-ANCA (+) patients compared to MPO-ANCA (+) had increased Scr at the time of diagnosis. The duration of clinical symptoms was similar in both, PR3 and MPO (+) patients, suggesting that renal involvement had a

more rapid course in PR3 (+) compared to MPO (+) patients. Renal biopsy findings were in agreement with the above, since in PR3 patients there was a prevalence of "active lesions" such as cellular crescents and mesangial hyperplasia.

The response to treatment was also different. PR3 patients started with increased serum creatinine levels, but responded to treatment quickly, demonstrating a rapid decline in serum creatinine, during the first month of the study.

Table 1: Differences between PR3 and MPO ANCA (+) patients at presentation and outcome

	MPO-ANCA n=9	PR3-ANCA n=13	p
M/F	4/5	10/3	NS
Age	61±12	51± 15	NS
Scr-diagnosis	5.2± 2.8	7.6± 5.2	NS
Scr-1st month	6.1± 3.3[a]	4.6± 2.8[c]	NS
Scr-end	5.1± 3.5[b]	5.2± 3.5[d]	NS
Proteinuria (g/24hr)	1.7± 1	1.5± 1.7	NS
Respiratory System			
Upper Respiratory Track	1/9 (11%)	5/13 (38%)	NS
Bilateral nodules on CT	1/7 (14%)	8/12 (67%)	0.02
"Ground glass" on CT	6/7 (86%)	6/12 (50%)	NS
Pulmonary Fibrosis	2/7 (28%)	0/12	0.05
Renal Biopsy			
Cellular crescents (%)	26±27	59±37	0.05
Fibrous crescents (%)	13±21	11±20	NS
Mesangial hyperplasia	0.2±0.4	1±0.8	0.01
Relapses	2/9 (22%)	9/13 (69%)	0.03
ESRD	2/9 (22%)	4/13 (31%)	NS
Deaths	6/9 (67%)	5/13 (38%)	NS

a: p(Scr-diagnosis versus Scr-1st month)=NS,
b: p(Scr-1st month versus Scr-end)=0.02,
c: p(Scr-diagnosis versus Scr-1st month)=0.02,
d: p(Scr-1st month versus Scr-end)=NS

MPO patients required a more prolonged therapy to achieve the same result, although they started with lower levels of serum creatinine. All the above findings, the acute histological lesions within PR3 patients, the increased Scr levels and the rapid response to treatment, have also been reported in previous studies[10,19,20]. These findings prompt us to hypothesize that PR3-ANCA (+) vasculitis in early stages undergoes an acute phase, which may quickly lead to ESRD, if remained untreated. In contrast MPO patients demonstrate a slower decline of renal function, which may gradually lead to ESRD, but respond only after a prolonged course of adequate treatment.

References

1. Jennette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitis. Proposal of an international consensus conference. Arthritis Rheum 1994, 37: 187-192
2. Jennette JC, Falk RJ: Antineutrophil cytoplasmic antibodies and associated diseases: A review. Am J Kidney Dis 1990, 18: 188-195
3. Jennette JC, Falk RJ Small-Vessel Vasculitis. N Engl J Med 1997, 337(21): 1512-1523
4. Falk RJ, Hogan S, Carey TS, et al: Glomerular disease collaborative network: clinical course of antineutrophil cytoplasmic antibody associated glomerulonephritis and systemic vasculitis. Ann Intern Med 1990; 113:656-663
5. Kamesh L, Harper L, Savage COS: ANCA- positive vasculitis. J Am Soc Nephrol 2002 ; 13(7) :
6. Ter Maaten JC, Fransen CFM, Gans ROB, Strack van Schijndel RJM, Hoorntje SJ: Respiratory failure in ANCA-associated vasculitis. Chest 1996, 110(2):357-363
7. Rodriguez W, Hanania N, Guy E, Guntupali J: Pulmonary-renal syndromes in the intensive care unit. Critical Care Clinics 2002, 18(4):
8. Gallagher H, Kwan J, Jayne D: Pulmonary renal syndrome: a 4-year, single center experience. Am J Kidney Dis 2002; 39(1):
9. Goldschiding R, Cohen Tervaert JW, Cans ROB, et al: Different immunological specificities and disease associations of C-ANCA and P-ANCA. Neth J Med 1990;36:114-116
10. Franssen CFM, Gans ROB, Arends B, et al: Differences between anti-myeloperoxidase and anti-proteinase 3 associated renal disease. Kidney Int 1995; 45:193-199
11. Gal AA, Salinas FF, Staton GW: The clinical and pathological spectrum of ANCA related pulmonary disease: a comparison between perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies. Arch Pathol Lab Med 1994;118:1209-1214
12. Akira M: Computed tomography and pathological findings in fulminant forms in idiopathic interstitial pneumonia. J Thorac Imaging 1999; 14:76-84
13. Davis AM, Johnson JE, Cruz-Gervis R, et al: Is vasculitis an early pathogenic mechanism of interstitial pulmonary fibrosis? Chest 2001; 120(1):
14. Eschum G, Mink S, Sharma S: Pulmonary interstitial fibrosis as a presenting manifestation in perinuclear antineutrophil cytoplasmic antibody microscopic polyangiitis. Chest 2003;123(1):
15. Hiromura K, Nojima Y, Kitahara T, et al: Four cases of anti-myeloperoxidase antibody related rapidly progressive glomerulonephritis during the course of idiopathic pulmonary fibrosis. Clin Nephrol 2000;53:384-389
16. Kondoh Y, Taniguchi H, Kawabata Y, et al: Acute exacerbation in idiopathic pulmonary fibrosis: analy-

sis of clinical and pathological findings in three cases. Chest 1993; 103:1808-1812
17. Vergunst CE, Van Gurp E, Hagen EC, et al: An index for renal failure in ANCA associated glomerulonephritis. Am J Kidney Dis 2003; 41(3):
18. Haworth SJ, Savage COS, Carr D, Hughes JMB, Rees AJ: Pulmonary hemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis. BMJ 1985; 290:1775-1778
19. Slot MC, Tervaert JWC, Franssen CFM, Stegeman CA: Renal survival and prognostic factors in patients with PR3 ANCA associated vasculitis with renal involvement. Kidney Int 2003; 63:670-677
20. Westman KWA, Bygman PG, Olson H, Ranstam J, Wieslander J: Relapse rate, renal survival and cancer morbidity in patients with Wegener's granulomatosis and microscopic polyangitis with renal involvement. J Am S Nephrol 1998; 9:842-852