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Different Outcome of the Renal and Pulmonal Disease in Wegener's Granulomatosis

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Abstract
Wegener's granulomatosis is a systemic necrotizing vasculitis which may have a fatal course even in the cases when effective therapy is administered. We investigated the clinical features and outcome of 5 patients with Wegener's granulomatosis. 4/5 patients presented with crescentic glomerulonephritis, one of them with necrotic form. Respiratory tract involvement was present in all cases. 3/5 patients responded favorably to immunosuppressive therapy, one of them with fatal relapse after 4 years. The other two patients died within two months because of irreversible pulmonary involvement. In conclusion, respiratory involvement is important for the patient survival and renal involvement for the kidney survival. Another important point, the survival rates of patients with WG on chronic hemodialysis are comparable to those of other patient groups with end stage renal disease.

Introduction
Wegener's granulomatosis (WG) is a systemic necrotizing vasculitis involving mainly the upper and lower respiratory tract and the kidneys. Without effective therapy the disease has a fatal course, with 82% of patients dying within one year [1, 2, 3]. The manifestation of WG in kidneys leads to a rapid progressive glomerulonephritis with extracapillary and intracapillary proliferation with cellular and fibrous crescents [2, 4]. Prior to the introduction of dialysis, uremia was the main cause of death in these patients. Using cyclophosphamide and steroids, the patients can be successfully treated with a 5-year survival rate between 60 and 90%. Nevertheless, 20-60% of the patients with renal involvement and elevated creatinine at the start of immunosuppressive therapy develop end-stage renal disease during a period of 5 years [5]. It has been speculated that, similar to the course of systemic lupus erythematosus, disease activity decreases after the loss of renal function. After kidney transplantation a reduction in vasculitis activity in patients with Wegener's granulomatosis was shown. However, chronic immunosuppressive therapy may account for this observation. Relapses of WG in the patients on chronic dialysis have been described, but the numbers of patients included are very small. Moreover, data are not available on the kind and dose of immunosuppressive therapy at the time of the relapse and on the outcome after treatment in chronically dialysed patients. In this study we retrospectively analyzed 5 patients with WG with renal involvement and their outcome.

Subjects and methods
5 cases with WG, 2 male and 3 female, aged 38.2±8.2, were detected at the Department of Nephrology, Clinical Center, Skopje. The diagnostic criteria, taking into account the definition of the International Consensus Conference at Chapel Hill for WG, were a typical presentation with involvement of the respiratory tract and a positive ANCA. ANCA tested by indirect immunofluorescence were found positive at least twice during the time course of the disease [4]. All sera were also tested with ELISA using proteinase 3 and myeloperoxidase as antigens. All patients underwent renal biopsy, optical and immunofluorescence microscopy was done in all of them, electron microscopy in two cases. Pulmonary involvement was documented using X-ray chest examination and computerized tomography. Relapses were defined as recurrence of first appearance of WG organ involvement of sufficient severity to require treatment. After the diagnosis had been established, the patients were treated with cyclophosphamide, oral application, 1-2mg/kg BW/day and steroids, starting with "pulse" therapy with methylprednisolone 1g/daily for three days and continuing with 0,5mg/kg/daily. The therapy with cyclophosphamide was tapered off to 0,7-1mg/kg BW/daily after 6 months and steroids to 20mg daily.

Results
As it can be seen all patients developed renal failure and significant proteinuria. Pulmonary involvement was present in all, upper respiratory system lesions in one patient. Outcome of the disease in different patients was different, so we will present them separately.
Patient 1: Pulmonary involvement resolved completely, serum levels of urea and creatinine decreased to normal ranges (urea - 5,7mmol/l, creatinine 96 micromol/l), as well as proteinuria (0,21g/daily). So we can conclude that remission in this patient was complete. The treatment was withdrawn after one year, the follow-up period, free of relapses, was 3 years.

Table 1: Clinical data of the patients at the biopsy

Patient	Gender	Age	Urea	Creatinine	Proteinuria g/d
1.	f	40	27,5	187	0,61
2.	f	30	12,6	171	2,56
3.	f	48	37,7	686	3,14
4.	m	44	37	430	4,09
5.	m	29	49	1880	1,6

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Table 2: Pulmonary and renal involvement

Patient	Respiratory tract	Renal involvement	ANCA
1.	Pulmonary granulomas	Crescentic glomerulonephritis	c-ANCA
2.	Pulmonary granulomas	Necrotizing glomerulonephritis	c-ANCA
3.	Pulmonary granulomas	Crescentic glomerulonephritis	c-ANCA
4.	Pulmonary granulomas	Crescentic glomerulonephritis	c-ANCA
5.	Rhinitis, sinusitis Pulmonary granulomas	Crescentic glomerulonephritis	c-ANCA

Patient 2: Incomplete recovery of pulmonary granulomas, with persistence of cystic formations. Complete recovery of renal function with decrease of serum levels of urea and creatinine to normal ranges (urea – 4,9mmol/l, creatinine – 65 mikromol/l), but persistence of non-nephrotic proteinuria, 0,45 g/daily. Follow-up period was one year, the patient was treated all the time.

Patient 3: There was no response to previously described immunosuppressive treatment, so plasma-exchanges and hemodialysis treatment were also performed. The patient died after two months because of cardio-respiratory insufficiency.

Patient 4: Complete remission of pulmonary involvement within two months, stable renal function during follow-up (4 years), with serum urea 7,9-9,6 mmol/l and serum creatinine 114-198 micromol/l and significant proteinuria 0,97-1,76g/d. After two years combined treatment with steroids and cyclophosphamide, the patient was only on cyclophosphamide 25mg daily during the further two years. Acute relapse, with severe pulmonary changes and acute deterioration of the renal function was observed after 4 years follow-up. Immunosuppresion failed, the patient was treated with hemodialysis, and he died after two weeks treatment because of severe respiratory failure.

Patient 5: Renal failure (acute oligoanuria) improved after immunosuppression, with slight decrease of serum levels of urea and creatinine (urea 24 mmol/l, creatinine 425 micromol/l) with complete disappearance of pulmonary granulomas. New relapse after 6 weeks treatment was followed by new pulmonary granulomas. The patient died because of severe respiratory failure.

Discussion

We presented a small group of patients with WG, with similar presentation at onset: severe pulmonary involvement, more that 80% crescents at renal biopsy, all c-ANCA positive with different outcome of the disease. It is interesting that our patients with poor prognosis died because of respiratory failure due to severe pulmonary granulomas, so none of our patients was treated with chronic dialysis. Data from the literature suggest strong correlation between renal histopathology changes and renal outcome in patients with WG [2, 4]. We found a positive correlation between serum creatinine and the fraction of active glomerular lesions (crescents, necrosis) and a negative correlation between serum creatinine and the fraction of normal glomeruli. Recent studies found the percentage of normal glomeruli to correlate with renal outcome, but did not find active glomerular lesion to be significantly correlated to the severity of the renal disease. 4/5 of our patients presented with classical crescentic glomerulonephritis, glomerular necrosis was noted in only one patient (now in remission). On the contrary, glomerular necrosis is a very frequent histopathological finding in the studies of other authors. Other authors also did not loose the patients so early, before start of chronic dialysis, may be due to better cardio-pulmonary assistance and better intensive care units. However, relapses in studies with patients on dialysis, led to involvement mainly of the upper and lower respiratory tract [5]. Most of the reported patients had general symptoms such as weight loss, fatigue and/or fever. Despite an early diagnosis of the relapse and the achievement of remission in most cases, one third of these patients with respiratory relapses developed irreversible damage. These reports stress that respiratory involvement is important for the patient survival and renal involvement for the kidney survival. Another important point, the survival rates of patients with WG on chronic hemodialysis are comparable to those of other patient groups with end stage renal disease [5]. The relapse rate during chronic dialysis treatment is not a more important risk factor than the risk factors in other renal diseases, for example vasculopathy in diabetic nephropathy, malignant hypertension etc.

References

1. Robinson AJ: Antineutrophil cytoplasmic antibodies (ANCA) and the systemic necrotizing vaculitides. Nephrol Dial Transplant 9:119-126, 1994.
2. Aasarod K, Bostad L, Hammerstrom J, Storker J, Iversen BM: Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. Nephrol Dial Transplant 16:953-960, 2001.
3. Geffriaud-Ricourad C, Noël LH, Chauveau D, Houhou S, Grűnfeld JP, Lesavre P: Clinical spectrum associated with ANCA of defined antigen specificities in 98 selected patients. Clin nephrol 39: 125-136, 1993.
4. Bajema IM, Hagen EC, Hermans J, Noël LH, Waldherr R, Ferrario F, Van der Woude FJ, Bruijn JA: Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. Kidney Int 56: 1751-1758, 1999.
5. Haubitz M, Koch KM, Brunkhorst R: Survival and vasculitis activity in patients with end-stage renal disease due to Wegener's granulomatosis. Nephrol Dial Transplant 13: 1713-1718, 1998.