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Short communication

Wegener's Granulomatosis with Renal and Pulmonary Involvement - Single Centre Experience

Ristovska Vesna[1], Grcevska Ladislava[1], Popovska-Milovancheva Maja[1], Nikolov Vladimir[1] and Polenakovic Momir[2]

[1]University Clinic of Nephrology, Medical Faculty, University "Sts. Cyril and Methodius" Skopje, Republic of Macedonia, [2]Macedonian Academy of Sciences and Arts, Skopje, R.Macedonia

Abstract

Introduction. Wegener's granulomatosis is a systemic necrotizing vasculitis with a potentially fatal course even in patients treated with immunosuppressive drugs. The disease is not very common but the true incidence is difficult to be determined.
Methods. We report 16 cases of Wegener's granulomatosis diagnosed at our Department during a 10-year period, between 1999 and2009. Patients age was 42.8+/-8.6 years, 9 of them were males and 7 females. All patients had severe renal and pulmonary involvement and positive ANCA. The respiratory tract involvement was characterized by multiple bilateral nodular cavitary infiltrates on the computed tomography. The characteristic lesion observed in the renal biopsy was extracapillary glomerulonephritis with crescents found in 80 % of patients.
Results. The clinical features of patients at diagnosis were the following: Upper respiratory tract infection was observed in 12 patients, pulmonary involvement in 15, conjunctivitis in 1, skin lesions in 9 patients, gastroduodenal granulomas in 1, proteinuria and hematuria in 15 and renal insufficiency in 13 patients. Although there were some differences in the clinical and laboratory findings at presentation, nearly all patients had haemoptysis, mild hypertension, leucocytosis, proteinuria and increase of serum creatinine. Fifteen out of 16 patients were treated with corticosteroids and one patient was treated by cyclophosphamide alone. In 80% of patients combination of corticosteroids with cyclophosphamide was used whereas plasmapheresis was applied in 9 of 16 patients (56%). Complete remission was observed in 3 patients, partial remission in 3 and end stage renal disease in 3 more patients. The remaining 7 patients did not survive. In 2 out of 9 patients (22%) treated by plasmapheresis, complete remission of the disease was achieved. No significant difference was observed in all the parameters examined between patients who showed remission and those who did not survive.
Conclusion. The clinical course of Wegener's granulomatosis with renal and pulmonary involvement might be poor despite the administration of immunosuppressive treatment. The early detection of the disease is very important and might be followed by a more favorable outcome.

Key words: Wegener's granulomatosis, glomerulonephritis, chronic renal failure

Introduction

Wegener's granulomatosis is a systemic necrotizing vasculitis, involving mainly the upper and lower respiratory tract and the kidneys. Without effective therapy the disease shows increased mortality rate since 82% of patients are not alive one year after the diagnosis [1-3]. The disease is not very common and the true incidence is difficult to be determined. Male-to-female ratio is 1:1. The disease can be seen at any age, but the mean age at the time of presentation is approximately 40 years old. About 15% of patients are less than 19 years old.
The kidneys are usually involved in Wegener's granulomatosis. A rapidly progressive glomerulonephritis with presence of extracapillary and intracapillary proliferation and cellular and fibrous crescents is observed in a large percentage of patients [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 patients with renal involvement and elevated serum creatinine at the time of initiation of immunosuppressive therapy developed end-stage renal disease during a period of observation of 5 years [5-7]. It has been speculated that, similarly to systemic lupus erythematosus, the activity of the disease decreases after the loss of renal function. Following kidney transplantation, reduction in the activity of the disease has been observed in patients with Wegener's granulomatosis and is probably due to the administration

Correspondence to: Vesna Ristovska, University Clinic of Nephrology, "Vodnjanska" 17, 1000 Skopje, R. Macedonia

of immunosuppressive therapy. Relapses of Wegener's granulomatosis in patients on chronic dialysis have been described, but the number of patients included in the published studies is very small. Moreover, data concerning the dose of immunosuppressive therapy at the time of the relapse and the outcome after treatment of dialyzed patients is not available.

The aim of the study was to present our experience on patients with Wegener's granulomatosis who were diagnosed and treated at the University Clinic of Nephrology in Skopje Republic of Macedonia over a period of 10 years, between 1999 and 2009.

Patients and methods

Sixteen patients with Wegener's granulomatosis, 9 males and 7 females, aged 42.8+/-8.6 years old, were detected at the Department of Nephrology in the period between 1999 and 2009. The diagnostic criteria were: a typical presentation with involvement of the respiratory tract and positive ANCA. ANCA tested by indirect immunofluorescence were found positive at least twice during the course of the disease [4]. All sera were also tested with ELISA, using proteinase 3 and myeloperoxidase as antigens. Our Department is the single Centre in Republic of Macedonia in which a renal biopsy is performed in order to diagnose kidney diseases. All patients signed an informed consent before the renal biopsy. Light microscopy and immunofluorescence were available for the biopsy sections of 12 patients; electron microscopy was used in 2 cases. In 2 patients renal biopsy was not performed. One of them showed a lesion on epiglottis that was biopsied and proved to be granuloma, and another one died the second day of his admission at the hospital, because of the aggressive course of his disease.

Pulmonary involvement was documented using X-ray chest examination and computed tomography.

Relapse was defined as recurrence of the original manifestation of Wegener's granulomatosis with organ involvement that needed re-administration of immunosuppressive treatment.

After the diagnosis had been established, the patients were treated with oral cyclophosphamide (1-2 mg/kg BW/day) and steroids starting with pulse therapy (methylprednisolone 1 g/daily intravenously for 3 days) followed by oral administration of steroids (0.5 mg/kg/daily). The dose of cyclophosphamide was tapered off to 0.7-1 mg/kg BW/daily after 6 months and that of steroids to 20 mg/daily. The administration of corticosteroids alone was followed by some symptomatic improvement, but had only little effect in the clinical course of the disease. Instead of oral administration of cyclophosphamide, we have also used given cyclophosphamide intravenously (500 mg IV every 4-6 weeks) in combination with corticosteroids (Pronison 30 mg /daily). Side-effects of treatment were rarely seen.

Haemodialysis was started in patients with advanced renal failure. Plasma exchange was performed 2-4 times weekly, sometimes every day [8]. Different protocols, depending on the severity of the disease were used for plasmapheresis.

Statistical analysis

For statistical analysis, Student's t-test was used to compare continuous variables and chi-squared test to compare discrete variables. Fisher exact probability test was also used. Any p value below 0.05 was considered as significant.

Results

All patients visited the outpatient Clinic for consultation because of significant proteinuria and impairment of renal function as well as pulmonary involvement. One patient had a lesion in the upper respiratory tract.

Table 1. Clinical manifestations of our patients

Clinical features	Number of patients
Upper respiratory tract infection	12
Pulmonary involvement	15
Conjunctivitis	1
Skin lesions - macula, papules	8
- subcutaneous nodules	1
Gastroduodenal polipoid granulomas	1
Haematuria, proteinuria	15
Renal failure	13

Table 2. Laboratory findings at the admission in the hospital

N	Leucocytes	Urea (mmol/l)	Creatinine (μmol/l)	Proteinuria (g/24 h)	ANCA
1.	15,2	37.7	686	3.14	(+)
2.	13,5	14.0	270	2.43	(+)
3.	12,4	27.9	187	0.61	(+)
4.	14,8	12.6	171	1,04	(+)
5.	20,5	30.3	1889	0.87	(+)
6.	6,0	5.5	74	0.06	(+)
7.	7,3	31.1	891	5.35	(+)
8..	13,0	31.5	1310	0.77	(+)
9.	15,1	28.9	1114	1.67	(+)
10.	15,1	12.0	134	0.92	(+)
11.	19,7	45.7	677	0.52	(+)
12.	13,7	55.3	1116	0.50	(+)
13.	20,2	31.4	801	2.83	(+)
14.	14,3	70	1704	3.26	(+)
15.	14,5	41.9	1116	2.28	(+)

16.	12,5	30.5	872	2.62	(+)

The clinical manifestations of all patients at the time of admission in the hospital are presented in Table 1.Upper respiratory tract infection was observed in 12 patients, pulmonary involvement in 15, conjunctivitis in 1, skin lesions in 9 patients, gastroduodenal granulomas in 1, proteinuria and hematuria in 15 and renal insufficiency in 13 patients. The laboratory investigation of all patients at the admission in the hospital is shown in Table 2. Although there were some differences in the clinical and laboratory findings at presentation, nearly all patients had haemoptysis, mild hypertension, leucocytosis, proteinuria and increase of serum creatinine.

The mean age of men with Wegener's granulomatosis at the time of presentation was 46+/-10.6 years and that of women 36.33+/- 9.85. This difference was not proved to be significant (p=NS).

The main histological finding in the renal biopsies performed, was extracapillary glomerulonephritis with crescents present in 80% of cases as it is shown in Table 3. We found association between the serum creatinin levels and the severity of active glomerular lesions (crescents, necrosis).

Table 3. Histologic findings on renal biopsy

N	G	Age	Histological findings on renal biopsy
1.	f.	48 y	Rapidly progressive glomerulonephritis- diffuse extracapillary
2.	m.	44 y	Rapidly progressive glomerulonephritis
3.	f.	40 y	Diffuse mesangioprolif.glomerulonephritis with fibrocellular crescents
4.	f.	30 y	Necrotizing glomerulonephritis with extracapillary lesions
5.	m.	29 y	Rapidly progressive glomerulonephritis-extracapillary lesions
6.	f.	39 y	Endocapillary and extracapillary glomerulonephritis
7.	m.	39 y	Rapidly progressive glomerulonephritis
8.	f.	41 y	Rapidly progressive glomerulonephritis
9.	f.	20 y	Rapidly progressive glomerulonephritis
10.	m.	40 y	Extracapillary proliferative glomerulonephritis
11.	m.	52 y	Rapidly progressive glomerulonephritis – extracapillary lesions
12.	m.	63 y	Extracapillary glomerulonephritis
13.	m.	55 y	Glomerulonephritis granulomatosa
14.	m.	48 y	Rapidly progressive glomerulonephritis

Table 4. Therapeutic regimen and prognosis

N	Corticosteroids	Cyclophosphamide	PE	HD	Prognosis
1.	MP, Decortin	(+)	(+)	(+)	Death
2.	Urbason	(+)	(+)	(+)	Death
3.	Pronison	/	/	/	Remission
4.	MP, Decortin	(+)	(+)	(+)	Remission
5.	MP, Urbason	(+)	(+)	(+)	Death
6.		(+)	/	/	Remission
7.	MP, Decortin	(+)	/	(+)	Death
8.	MP, Decortin	/	/	(+)	CHD
9.	MP, Decortin	/	/	(+)	Death
10.	MP, Decortin	(+)	/	/	Remission
11.	MP	/	(+)	(+)	Death
12.	MP	(+)	(+)	(+)	Death
13.	MP, Decortin	(+)	(+)	(+)	CHD
14.	MP, Decortin	(+)	(+)	(+)	Remission
15.	MP, Decortin	(+)	(+)	(+)	CHD
16.	MP, Decortin	(+)	(+)	(+)	Remission

MP-metylprednisolone, PE plasma exchange, HD-haemodialysis, CHD-chronic haemodialysis

The therapeutic regimens used and the prognosis of the disease in all patients are shown in Table 4. Fifteen out of 16 patients were treated with corticosteroids and one patient was treated by cyclophosphamide alone. In 80% of patients cyclophosphamide was used in combination with corticosteroids whereas plasmapheresis was applied in 9 of 16 patients. Complete remission was observed in 3patients, partial remission in 3 and chronic haemodialysis was started in 3 patients. The remaining 7 patients did not survive. In 2 out of 9 patients treated by plasmapheresis, complete remission of the disease was achieved. No significant difference was observed in all the parameters examined between patients who showed remission and those who did not survive.

Discusion

In this study we present a group of patients with Wegener's granulomatosis and severe renal and pulmonary disease. The clinical outcome of the disease was different despite the same immunosuppressive regimen used in all patients. It is worth mentioning that our patients with poor prognosis died because of respiratory failure, due to severe pulmonary disease. Literature data suggest a strong correlation between renal histopathology changes and renal out-

come in patients with Wegener's granulomatosis [2,4]. In recent studies, the percentage of normal glomeruli has been found to be correlated to renal outcome, but the presence of active glomerular lesion has not been significantly correlated to the severity of renal disease. Most of our patients presented with classical crescentic glomerulonephritis whereas glomerular necrosis was noticed in only one patient (now in remission). However, glomerular necrosis has been very frequently found in other studies.

Older age and elevated serum creatinine levels at diagnosis, predicted a poor prognosis [5,9]. Most of the reported patients had general symptoms like weight loss, fatigue and/or fever. In patients on dialysis with relapses, involvement mainly of the upper and lower respiratory tract has been observed. Despite the early diagnosis of the relapses and achievement of remission in most cases, about one third of patients with respiratory relapses developed irreversible damage. These reports have stressed the fact that respiratory involvement is important for the patients' survival and renal involvement for the kidney survival. The survival rates of patients with Wegener's granulomatosis on chronic haemodialysis were comparable to those of other patients' groups with end-stage renal disease.

Survival in Wegener's granulomatosis increased dramatically after the establishment of cyclophosphamide and corticosteroids as the standard therapeutic regimen. However, Wegener's granulomatosis is still related with increased mortality rate whereas most patients develop permanent organ damage [10].

In conclusion, our findings suggest that early detection of the disease, when respiratory involvement is not severe is very important. Every patient with haematuria and symptoms of respiratory tract involvement should be immunologically tested and treated properly. However, the clinical course of the disease is not predictable and a large number of patients shows and unfavorable outcome.

Conflict of interest statement. None declared.

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