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RENAL HISTOPATHOLOGY AND CLINICAL COURSE IN PATIENTS WITH WEGENER'S GRANULOMATOSIS – SINGLE CENTRE EXPERIENCE FROM THE REPUBLIC OF MACEDONIA

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A b s t r a c t: The aim of this study was to evaluate the clinical course of patients with Wegener's granulomatosis (WG) with renal involvement, to examine histopatological form seen in renal biopsies and present follow-up of the patients.

A retrospective analysis was carried out of 18 patients presenting with WG and active renal disease at the University Nephrology Department, Ss. Cyril and Methodius University, Skopje, R. Macedonia. All patients were ANCA positive and had a percutaneous renal biopsy taken on their admission.

12 patients were male, 6 female, aged 48.61 ± 13.77 (M ± SD). All had extrarenal symptoms prior to admission. Oligoanuria was present in 7/18 (38.9%) of the patients, serum urea levels of the whole group were 40.67 ± 18.13 mmol/l(M ± SD) and for serum creatinine 691.06 ± 384.93 μmol/l (M ± SD). Necrotizing glomerulonephritis with crescents was present in 11/18 (61.11%) of the patients, the others presented diffuse proliferative extracapillary glomerulonephritis. All patients were treated with steroids and cyclophosphamide, and plasmapheresis was performed in 7/18 (38.9%) of the patients. Probability rate for surviving after one month was 0.6111 and after three months 0.3889 (Kaplan-Meier).

The current treatment of WG in our study did not prevent serious complications and development of ESRD in a large number of our patients. This systemic disor-

der is still a serious problem and early diagnosis and alternative strategies for the management of the disease will be an important objective for further studies.

Key words: Wegener's granulomatosis, renal histopathology, crescents, necrotizing glomerulonephritis, granulomatous inflammation, clinical course.

Introduction

Wegener's granulomatosis (WG) was first distinguished as a clinical entity by Friedrich Wegener in 1936, but the first well-explained cases of WG were described between 1947 and 1958 as "an illness characterized by symptoms of progressive ulceration in the respiratory tract together with signs of widespread inflammatory disease, histological examination of material from each shows disseminated granulomata, most common in the respiratory tract and kidneys, and widespread vascular lesions similar to polyarteritis nodosa" [1, 2]. It is now clear that WG is a rare disease characterized by disseminated granulomatous vasculitis which primarily affects the upper and lower respiratory tract and the kidneys [3–11]. Other organ systems can also be affected, including eyes, ears, skin, joints, bones, salivary glands, thyroid, heart, liver, colon and intestinum [12–22]. Systemic clinical features (fever, fatigue, arthralgias) similar to those present in viral diseases can also be found. The epidemiology of WG is largely unknown, the incidence is low, and it seems that the disease is more frequent in the northern countries [6, 8, 9, 11, 23–26].

Antineutrophil cytoplasmic antibodies (ANCA), a new family of autoantibodies directed against various components of the neutrophil cytoplasm, are now regarded as a serological marker for renal-limited necrotizing and crescentic glomerulonephritis or associated with systemic vasculitis such as WG or other vasculitides [27–31]. The disease in WG runs a rapidly progressive course which usually leads to death within a few months (sometimes within weeks or days) unless treated with immunosuppressive therapy. The manifestation of WG in the kidneys leads to a rapid progressive glomerulonephritis with extracapillary and intracapillary proliferation or necrotizing glomerulonephritis with cellular and fibrous crescents [1, 11, 25, 28, 29, 30, 32]. Prior to the introduction of dialysis, uraemia 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 [33–39].

The disease is rare in the Republic of Macedonia (2 000,000 people), with frequency increasing during the past few years. In this study we retro-

spectively analysed 18 (12 male and 6 female) patients with WG, documented histologically, with respect to patient survival. We studied the organ pattern involved and the response to treatment.

Patients and methods

Patient selection

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 upper/lower respiratory tract (all our patients had pulmonary granuloma), positive ANCA and granulomatous inflammation in the histology (renal histopathology in our study) [9].

Methods

Antineutrophil cytoplasmic autoantibodies (ANCA) were tested by indirect immunofluorescence and with ELISA using proteinase 3 and myeloperoxidase as antigens.

Pulmonary granuloma were confirmed using chest radiography and computerized tomography, presenting as nodules, cavities or infiltrates.

Renal biopsy was performed in all presented patients, using the standard procedure for preparing renal biopsy specimens for optical and immunofluorescence microscopy. Diffuse proliferative glomerulonephritis with crescents, or necrotizing pauci-immune glomerulonephritis with interstitial granuloma, were confirmed in all presented cases.

All clinical data about pulmonary and renal involvement (and the other affected organs) were obtained from in-patient and out-patient files.

Treatment included a high dose of steroids (pulse therapy with methylprednisolone i.v. 0.5–1gr daily over three consecutive days, continuing with prednisone orally 0.5mg/kg daily) and pulse therapy with cyclophosphamide 0.5–1gr daily at the start, and after the first and third week. Plasmapheresis was performed in some patients with severe clinical features using a regime of 2 l exchanges per day with replacement by fresh frozen plasma. The number of plasma exchanges depended on the severity of the disease. The dose of prednisone was reduced to 20mg/day by 3 months. Cyclophosphamide pulses were continued monthly during the first 6 months, and every three months later, during the first year.

The whole follow-up period for the patients who survived the initial attack of the disease was 2 months – 8 years.

Relapses were defined as recurrence of WG organ involvement of sufficient severity to require treatment.

Statistics

The values are given as the mean ± standard deviation (M ± SD). The survival rates were calculated according to Kaplan-Meier.

Results

Table 1

Clinical features at presentation (excluding renal involvement)

Patient	Sex	Age	Extrarenal clinical features	Duration prior to admission
1.	female	32	fever, sinusitis, cough	6 months
2.	male	62	cough, haemoptysis	one month
3.	male	47	fever, weakness, cough	one month
4.	female	41	fever, weight loss, sinusitis, arthralgia, necrosis of the adipose tissue of legs	4 months
5.	male	58	cough, haemoptysis	2 weeks
6.	male	55	periodical cough and haemoptysis	one year
7.	male	55	weight loss, arthralgia	3 months
8.	male	36	sinusitis, otitis, cough, dyspnoea, attacks of extensive gastrointestinal bleeding	4 months
9.	male	55	fever, dyspnoea	6 months
10.	female	66	cough	2 months
11.	male	63	fever, cough, dyspnoea laringeal pain	one week
12.	male	52	cough, dyspnoea, haemoptysis	2 months
13.	female	49	cough, haemoptysis	one month
14.	male	68	cough, dyspnoea	one month
15.	female	47	weight loss	4 months
			cough, dyspnoea, haemoptysis	one week
16.	female	29	cough, granuloma in adipose tissue of legs	4 months
17.	male	19	fever, arthralgias, dyspnoea, cough, haemoptysis	2 weeks
18.	male	56	cough, dyspnoea	one week

12 patients were male, 6 female, aged 19–68 years, 48.61 ± 13.79 (M ± SD). It seems that the female patients were younger, but because of the small number of patients this fact was not confirmed. Symptoms of the upper and lower respiratory system, as first clinical signs, were present in 17/18 (94.4%) of the

patients, systemic clinical features (fatigue, fever, arthralgia) in 8/18 (44.44%), necrosis of the adipose tissue of the legs (2/18, 11.11%) and extensive gastrointestinal bleeding because of the ulcerated granulomata of the gastrointestinal system (1/18, 5.56%) were rare. The period of duration of the extrarenal symptoms was variable, between one week and 6 months, 2.61 ± 2.51 (M ± SD) months.

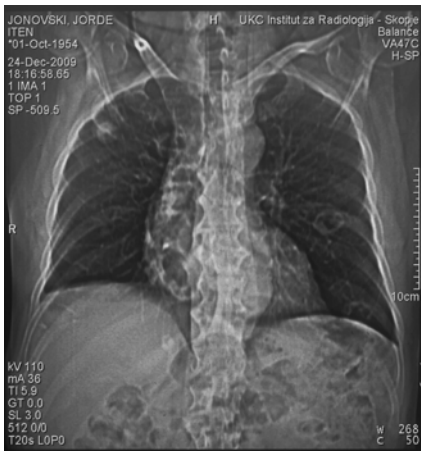

Figure 1– Computerized tomography of the chest with visible granulomata

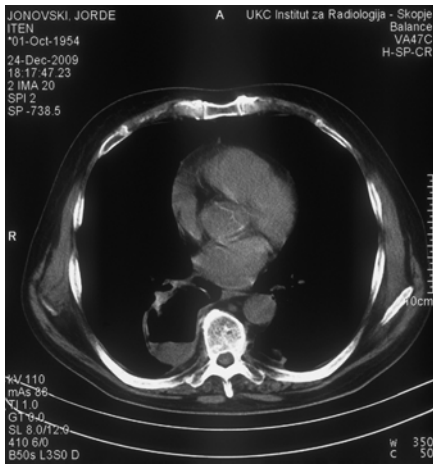

Figure 2 – Large excavated pulmonary granuloma on chest CT

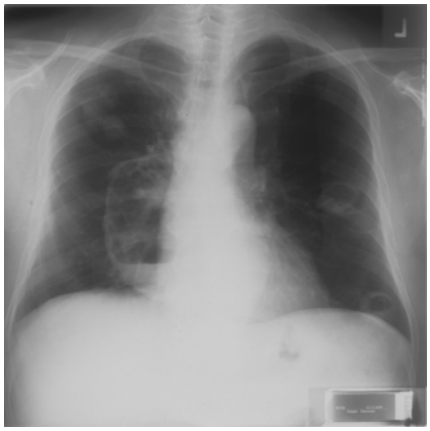

Figure 3 – Chest radiography: large paracardial excavated granuloma

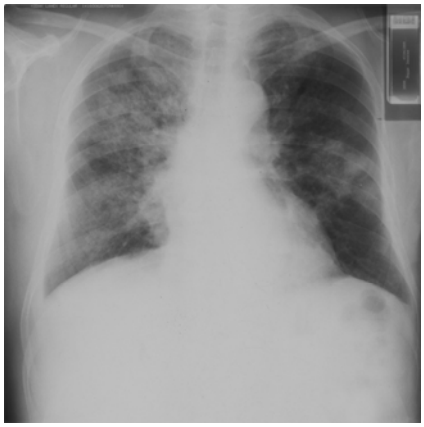

Figure 4 – Chest radiography: diffuse pulmonary infiltration

Table 2

Renal disorders at admission

Patient	Oligoanuria	Serum levels of urea mmol/l	Serum creatinine μmol/l	Proteinuria g/d	Haematuria/ erythruria
1.	–	34,3	362	1,04	+
2.	–	27,1	741	1,24	+
3.	–	18,6	433	0.17	–
4.	–	32,8	392	2,4	+
5.	+	56	939	–	+
6.	+	65	761	–	+
7.	–	17,6	348	4.5	+
8.	+	30,5	872	–	+
9.	–	41	1116	2,28	+
10.	–	20,9	265	0,28	+
11.	+	70	1704	–	–
12.	–	56,3	801	1,7	+
13.	–	39	611	5,15	+
14.	+	37	300	2,8	+
15.	–	40	1144	1,67	+
16.	–	19	310	1,8	+
17.	+	76,8	1100	–	+
18.	+	39	780	–	+

• Proteinuria was not measured in patients with daily urine output less than 200 ml (patients: 5, 6, 8, 11, 14, 17 and 18).

Oligoanuria with acute renal failure was present in 7/18 (38.9%) of the patients at admission, serum levels of urea of the whole group at the start of treatment were 40.67 ± 18.13 mmol/l (M ± SD) and for serum creatinine 691.06 ± 384.93 μmol/l (M ± SD). In patients with daily urine output more than 200 ml proteinuria ranged from normal value (patient 3) to nephrotic ranges (patients 7, 13).

Table 3

Renal histopathological features, histopathological examinations of other tissues if done

Patient	Form of glomerulonephritis	Renal granuloma	Other organs and systems
1.	Necrotizing GN with crescents	+	–
2.	Diffuse proliferative GN with crescents	+	–
3.	Necrotizing GN with crescents	+	–
4.	Diffuse proliferative GN with crescents	+	Granulomatous inflammation of skin with necrosis
5.	Necrotizing GN with crescents	+	–
6.	Diffuse proliferative with crescents	+	–
7.	Necrotizing GN with crescents	+	–
8.	Diffuse proliferative GN with crescents	+	Granulomatous inflammation detected in biopsies of the gastrointestinal system (gastric and colonic granulomata)
9.	Necrotizing GN with crescents	+	–
10.	Necrotizing GN with crescents	+	–
11.	Necrotizing GN with crescents	+	–
12.	Necrotizing GN with crescents	+	–
13.	Diffuse proliferative GN with crescents	+	–
14.	Necrotizing GN with crescents	+	–
15.	Necrotizing GN with crescents	+	–
16.	Diffuse proliferative GN with crescents	+	–
17.	Diffuse proliferative GN with crescents	+	–
18.	Necrotizing GN with crescents	+	–

Necrotizing glomerulonephritis with crescents was present in 11/18 (61.11%) of the patients, the others presented diffuse proliferative extracapillary glomerulonephritis. Renal granulomata (as an inclusion criterion) were present in all cases. Histological examination of other tissues was performed in two patients (patients 4 and 8).

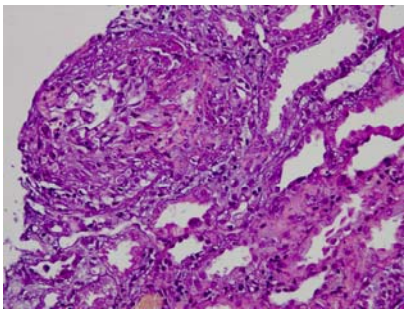

Figure 5 – Fibrinoid necrosis ("sun-burst" lesion) in affected glomerulus (HE, × 200)

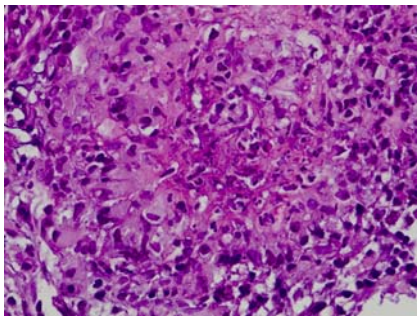

Figure 6 – Granulomatous change of affected glomerulus (HE, × 400)

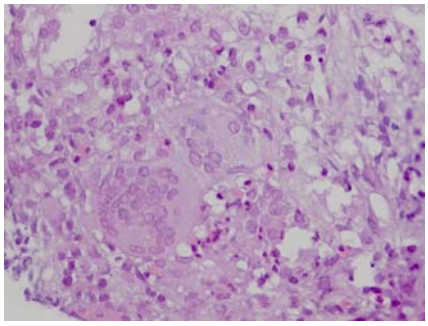

Figure 7 – Giant cell in interstitial granuloma (HE, × 400)

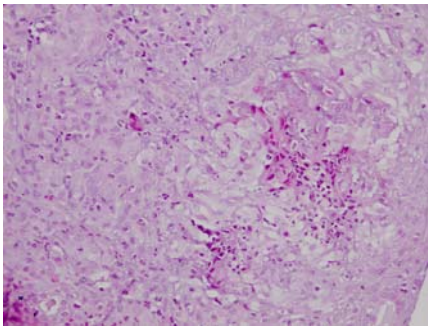

Figure 8 – Interstitial granuloma (HE, × 200)

Table 4

Response to treatment and follow-up

Patient	Treatment	Response to treatment	Follow-up period	Outcome
1.	steroids cyclophosphamide	remission of pulmonary involvement	6 months	without progression of renal involvement
2.	steroids cylophosphamide	remission of pulmonary and renal involvement	1 year	complete remission
3.	steroids cyclophosphamide	remission of pulmonary and renal involvement	8 months	complete remission
4.	steroids cyclophosphamide	remission of pulmonary involvement	3 months	progression to ESRD
5.	steroids cyclophosphamide	without response, death because of failure of respiratory system		
6.	steroids cyclophosphamide	remission of pulmonary involvement	2 months	improvement of renal failure
7.	steroids cyclophosphamide	remission of pulmonary involvement but progression to ESRD		
8.	steroids, PE cyclophosphamide	remission of pulmonary involvement	1 year	improvement of renal failure, relapses of disease of the gastrointestinal system
9.	steroids, PE cyclophosphamide	partial remission of pulmonary involvement	1 year	progression to ESRD persistent pulmonary granulomata
10.	steroids cyclophosphamide	remission of pulmonary involvement but progression to ESRD		
11.	steroids, PE cyclophosphamide	remission of pulmonary involvement and improvement of renal function	2 years	improvement of the the renal failure

12.	steroids, PE cyclophosphamide	remission of pulmonary involvement but progression to ESRD		
13.	steroids, PE cyclophosphamide	remission of pulmonary involvement but progression to ESRD		
14.	steroids cyclophosphamide	death because of gastrointestinal bleeding		
15.	steroids cyclophosphamide	remission of pulmonary involvement but progression to ESRD		
16.	steroids, PE cyclophosphamide	remission of pulmonary and renal involvement	8 years	complete remission
17.	steroids cyclophosphamide	death because of respiratory failure		
18.	steroids, PE cyclophosphamide	remission of pulmonary involvement	2 months	improvement of renal failure

*ESRD – end stage renal disease *PE – plasma exchange

Treatment with high doses of steroids and "pulse" therapy with cyclophosphamide i.v. was performed in all patients, and plasmapheresis in 7/18 (38,9%). Haemodialysis was necessary in 9/18 (50%) of the patients at the start of treatment. Three patients died during the first two weeks of the treatment, two of them because of respiratory failure (pulmonary granulomatosis did not respond to therapy) and one because of extensive gastrointestinal bleeding. Complete recovery of the pulmonary granulomata was noted in 14/18 (77.78%) of the patients, and partially in one, but 5/18 (27,78%) of the patients progressed to end stage renal disease during in-patient treatment. 10/18 (55,56%) patients continued with follow-up, 3/10 are in complete remission (normal renal function), 4/10 presented improvement of the renal function (renal failure without need for renal replacement therapy), patient number 1, who had stable renal failure at admission, did not progress to ESRD; and 2/10 patients progresssed to ESRD during follow-up. More of the patients who died, or progressed to ESRD either during admission or during follow-up, had necrotizing glomerulonephritis, but patient number 3, who also had necrotizing glomerulonephritis, presented complete recovery of the renal function. 5/11 glomeruli of this patient were normal on biopsy, 3 were partially and 3 completely necrotized.

Survival of the patients estimated by the Kaplan-Meier survival curve is presented in Fig. 9. Probability rate for surviving (survival of the patient or renal survival) after one month was 0,6111 and after 3 months 0,3889.

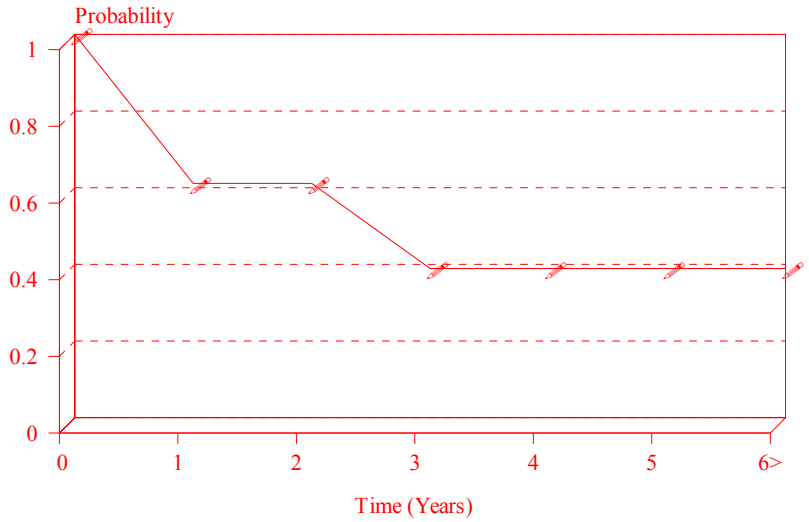

Figure 9 – Survival of the patients estimated by Kaplan-Meier

Discussion

We present 18 patients with WG diagnosed during the past decade at our Department, a referral centre covering an area with 2,000,000 people. It is interesting that we were not able to diagnose this disorder previously, may be because of the absence of the disease in this area, or late admission of the patients with end-stage renal failure and unexplained death because of respiratory failure. The epidemiology of WG is largely unknown. The incidence is low, diagnostic criteria vary, and studies often come from referral hospitals introducing the possibility of selection. The reported annual incidence varies between 0.4 per million in the 1970s and 8.5 per million in the 2000s, and annual incidence rates of 3 to 14 per million in European countries in 2009 [2, 8, 9, 11]. The disease is more frequent in northern countries, especially in the north of Europe, than in the south or in Asia; the estimates have increased over the last decade, which may be attributed to an increased awareness of the disease among clinicians, but also to the introduction of assays for anti-neutrophil cytoplasmic autoantibodies (ANCA) in 1985 [3, 4]. Positivity for ANCA was an inclusive criterion for our patients. We noted male predominance and different age of affected persons, but most of the patients were between the ages of 41 and 66. This contributes to the fact that WG most commonly occurs in the elderly (median age 55–70 years) [24].

Often starting as a limited disease with granulomatous inflammation in the upper airways, it proceeds to a systemic vasculitis with multi-organ involvement [1–6, 8, 12, 14, 16, 19, 20]. The first clinical signs of the disease in all our patients were extrarenal (upper and lower respiratory system, systemic disorders and symptoms of the gastrointestinal system), so they were admitted to our Department after various periods of time (between one week and 6 months). Renal affection and granulomata of the respiratory tract, sometimes with serious complications [40–42], are common for WG, but various organ involvement is also one of the main characteristics of the disease, affecting the gastrointestinal tract (oesophageal, colonic, hepatic granulomata), and the pancreas, thyroid, cardiac, salivary glands, ocular, otologic and bone involvement [12, 14, 16, 19, 20]. Our patient number 8 had pharyngeal, laringeal, oesophageal, gastric and colonic ulcerated granulomata with attacks of extensive gastrointestinal bleeding. Taking into consideration previously reported data, affection of the upper and lower respiratory tract is more common in patients from northern countries, and affection of the gastrointestinal tract in patients from southern countries. "Non-renal" WG is known in the literature, but we have no data about this form in our population, all our patients had renal involvement. The proportion of patients with renal involvement at disease presentation has varied between studies from < 20% to 80%, but invariably increases to 80–94% during follow-up, [4, 5, 6, 8, 10, 24] so does the "non-renal" form exist?

A typical renal characteristic of WG is crescentic, necrotizing glomerulonephritis with little or no immune deposits. These changes are not specific for WG, and can be also seen in other vasculitides and idiopathic necrotizing crescentic glomerulonephritis without evidence of extrarenal vasculitis [1, 2, 25, 28–30, 32, 39]. Necrotizing crescentic glomerulonephritis was dominant in our group of patients (11/18), but 7/11 patients presented diffuse proliferative glomerulonephritis with crescents. In other studies of ANCA-associated vasculitides, renal biopsies have demonstrated segmental necrosis in 98–100% and varying degrees of extracapillary proliferation in 85–94% [32, 39]. Interstitial granulomata (only one was enough) were found in all of our reported patients, they were selected for the study according to this criterion, as was mentioned previously.

Other forms of renal involvement such as renal limited WG and WG presenting as a renal mass were also described, but only as case reports [43, 44].

The outcome for our patients was worse than that reported in the other studies, we lost 3 patients during admission (because of other systems involvement) and only 8/18 (44,44%) of the others did not progress to ESRD during the admission and follow-up. Andrassy and co-workers found that 29% developed ESRD, but the follow-up period was short [45]. It is interesting that we did not note relapses of the renal disease during the follow-up in the patients who had

achieved remission of the disease. Pulmonary granulomata are still present in patient number 9 who has been on haemodialysis for the past year and on continuous immunosuppressive treatment. Patient number 8 has stable renal failure, but with relapses of the involvement of the gastrointestinal tract. Our data did not confirm earlier reports that WG is a frequently relapsing disease, but they confirm that in patients with renal involvement the mortality rate is high and chronic renal failure develops in a considerable fraction of the patients. We performed the classical method of treatment of our patients. Conventional immunosuppression for systemic vasculitides is limited by substantial side effects, cumulative drug toxicity and refractoriness in some patients, so new strategies of treatment such as mycophenolate mofetil, anti-adhesion molecule therapy, monoclonal antibody therapy and immuno-absorption were of benefit in some studies [46–50]. It will be good if we can apply new therapy regimens in future studies, and then compare the results of the outcome.

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Резиме

РЕНАЛНАТА ХИСТОПАТОЛОГИЈА И КЛИНИЧКИОТ ТЕК НА ПАЦИЕНТИ СО ГРАНУЛОМАТОЗА НА WEGENER – ИСКУСТВО НА ЦЕНТАР ОД РЕПУБЛИКА МАКЕДОНИЈА

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Извадок: Целта на оваа студија е да се евалуира клиничкиот тек кај пациенти со грануломатоза на Wegener и ренално оштетување, да се истражи хистопатолошката форма видена на реналната биопсија и да се прикаже следењето на болните.

Беше направена ретроспективна анализа на 18 пациенти со грануломатоза на Wegener и активна ренална болест на Клиниката за нефрологија, Скопје, Р. Македонија. Сите пациенти беа АНЦА позитивни и кај сите беше направена ренална биопсија по приемот.

Од машки пол беа 12 пациенти а 6 од женски, на возраст од 48,61 ± 13,77 (M ± SD). Кај сите пред приемот постоеја екстраренални симптоми. Олигоанурија беше присутна кај 7/18 (38,9%) од пациентите, со средна вредност за уреа за целата група од 40,67 ± 18,13 ммол/л (M ± SD) и серумски креатинин од 691,06 ± 384,93 микромол/л (M ± SD). Некротизантен гломерулонефрит со полумесечести формации беше присутен кај 11/18 (61,11%) од пациентите, другите се презентираа со дифузен пролиферативен екстракапиларен гломерулонефрит. Сите пациенти беа третирани со стероиди и циклофосфамит, а плазмафереза беше применета кај 7/18 (38,9%) од пациентите. Стапката на веројатност за преживување по еден месец изнесуваше 0,6111 и по 3 месеци 0,3889 (Kaplan-Meier).

Актуелната терапија на грануломатозата на Wegener не успеа да ги спречи сериозните компликации и да го превенира развојот на терминална хронична бубрежна инсуфициенција кај голем број од нашите пациенти. Ова системско нарушување сè уште е сериозен проблем и други стратегии за лекување на ова заболување би биле предмет на наредните студии.

Клучни зборови: грануломатоза на Wegener, ренална хистопатологија, полумесечести формации, некротизантен гломерулонефрит, грануломатозна инфламација, клинички тек.

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