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Assessment of clinical and diagnostic indicators of Grunulematosis with Polyangiitis

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Abstract. Granulomatosis with polyangiitis (GPA)(Wegener's) is a disease from the group of systemic vasculitis, which is characterized by necrotizing granulomatous inflammation and necrotizing vasculitis of small vessels with a predominant lesion of the upper respiratory tract, lungs and kidneys.

The study involved 60 patients (29 men and 31 women) aged 18 to 80 years with an established diagnosis of GPA. The average age of the examined patients was 48.9 ± 15.6 years. The diagnosis of GPA (n = 60) was established in accordance with the nomenclature adopted in 2012 at the conference in Chapel Hill (USA), as well as on the basis of the presence of at least 2 of 4 criteria of the American College of Rheumatology (ACR), 1990. [7] To confirm the diagnosis of GPA, a biopsy was performed in 40 (66.7%) patients: nasal mucosa or paranasal sinuses - in 17 (28.3%) patients, laryngeal formation - in 5 (8.3%) patients, orbital biopsy - in 12 (20.0%), skin - in 1 (2.3%), tympanic cavity - in 1 (2.3%), lungs - in 1 (2.3%), bronchi - in 1 (2.3%), conjunctiva - in 1 (2.3%). The average period from the onset of the disease to the diagnosis and initiation of treatment was 18.3 ± 32.32 months. At the time of the survey, the average duration of GPA in years was 5.7 ± 4.8 (in months 69.6 ± 57.7). 22 out of 60 patients had a local form of HPA (damage to the upper respiratory tract, the organ of hearing and vision). The local form was diagnosed in 7 men and 15 women aged 18 to 70 years (median age 47.5 years). The relapse rate was quite high in both cohorts, but in the prospective cohort it slightly decreased (from 66.2 to 54.2 per 100 patient-years) due to patients with generalized HPA. In the structure of exacerbations of diseases in both cohorts, small relapses prevailed (79.7% in the retrospective and 92.7% in the prospective). The frequency of large relapses in the prospective cohort decreased by about 2 times in patients with both generalized and localized HPA. The data obtained indirectly confirm the effectiveness of more "sparing" immunosuppressive therapy (methotrexate, azathioprine, glucocorticosteroids only), which we have begun to use more often in recent years.

Keywords: granulomatosis with polyangiitis, clinical features, diagnosis, treatment

Granulomatosis with polyangiitis (GPA) is a systemic vasculitis characterized by the development of granulomatous inflammation and necrotizing vasculitis of small vessels with a predominant lesion of the upper respiratory tract, lungs and kidneys. GPA remains one of the most severe and prognostically unfavorable systemic vasculitis. In recent years, there has been a tendency to an increase in the number of patients with HPA, which may reflect not only an improved long-term prognosis because of immunosuppressive therapy, but also a true increase in morbidity [1].

The prevalence of this pathology is 0.5-0.85 cases per 100 thousand of the population. The disease can occur at any age (the age range ranges from 5 to 90 years), in about 15% of cases it begins before the age of 20. The average age is 25-45 years. GPA equally affects men and women; it is most common among representatives of the Europeoid race (97%) and rarely occurs in individuals of the Negroid race (2%) [1,2].

Early diagnosis of HPA is a difficult clinical task and requires a thorough examination of the patient using modern research methods to identify pathognomonic symptoms. A targeted search for a lesion of the respiratory tract with rhinoscopy, laryngoscopy, computed tomography of the paranasal sinuses (PNS) and lungs is necessary, since for a long time the disease can be asymptomatic or be accompanied by meager clinical symptoms. Only in 50% of patients, the diagnosis is verified in the first 3-6 months from the onset of the disease, and in 7% of the HPA remains undifferentiated within 5-16 years from the onset of the first symptoms [3].

The need for timely diagnosis of HPA is dictated by the need for an early start of aggressive therapy. The main goal of therapy is to suppress the immunopathological reactions underlying the disease in order to achieve complete remission. Treatment is divided into three stages: induction of remission (short course of aggressive therapy), maintenance of remission (long-term therapy with immunosuppressants), and treatment of relapses [4]. Due to the variety of clinical manifestations and the severity of the prognosis, the choice of management and treatment tactics for patients with HPA always presents difficulties [5].

Materials and methods. The study included 60 patients with HPA, established in accordance with the criteria of the American College of Rheumatology 1990 and the nomenclature adopted in 2012 at a conference in Chapel Hill (USA) [6]. The patients were observed in a multidisciplinary clinic of the Tashkent Medical Academy.

The general examination of the patients was carried out according to the plan adopted in the clinic. When studying the anamnesis, special attention was paid to the presence of disease activity, the presence of lesions of various organs and systems. The BVAS scale (Birmingham vasculitis activity index) was used to assess the activity [7,23]. Remission of the disease was considered the presence of 1 or less points on the BVAS scale, exacerbation of HPA - 2 or more points on the BVAS scale. In all patients, organ lesions were assessed using the VDI index [8]. When assessing the index of damage, organ damage that has been observed since the onset of vasculitis is taken into account. Patients often have pre-vasculitis comorbidities that should not be considered. Manifestations of active vasculitis are recorded using the BVAS scale.

When analyzing the course of the disease, a local (lesion of the upper respiratory tract, organ of vision and hearing) and generalized (damage to the upper respiratory tract, organ of vision and hearing in combination with damage to the lungs and / or kidneys, as well as the gastrointestinal tract, nervous system, skin) variants of HPA. Generalized HPA includes early systemic, generalized and severe variants of the disease, which are isolated in accordance with the classification of the European

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Society for the Study of Vasculitis (EUVAS) [9,10]. All patients were assessed for signs of vasculitis and / or granulomatosis [11, 12, 13, 14] (Tab. 1).

Table 1.

Criteria of vasculitis and granulomatous inflammation

Criteria of vasculitis	Criteria of granulomatous inflammation
1. Glomerulonephritis Hematuria or hematuria in combined with proteinuria Histological picture of focal segmental low-immune glomerulonephritis with crescents	1. Granulomatous inflammation on biopsy
2. Extrarenal vasculitis: Cutaneous vasculitis Episclerite Multiple mononeuritis	2. Infiltrates / nodes in the lungs: persistent (more than 1 month) with decay, formation cavities and / or stenosing endobronchitis
	3. Damage to ENT organs or eyes: Perforation of the nasal septum Destructive sinusitis Sublining stenosis of the larynx or trachea Orbital pseudotumor Polypoid thickening of the mucosa sinuses, mastoiditis (lasting at least 3 months)

ANCA was determined by indirect immunofluorescence (antibodies were detected in 20 people), and subsequently by enzyme immunoassay (antibodies to proteinase 3 were detected in 16 patients, antibodies to myeloperoxidase - in 16, antibodies to both antigens - in 5).

Morphological examination with confirmation of the diagnosis was carried out in 189 (78%) patients, of whom in 6 cases the diagnosis of granulomatosis with polyangiitis (Wegener's) was established according to autopsy data. Lifetime diagnosis of the disease was carried out by morphological examination:

- nasal mucosa in 106 people;
- orbital tissues in 30 patients;
- contents of maxillary sinuses in 9 people;
- skin and subcutaneous tissue in 8 patients;
- lung tissue in 8 people;
- the mucous membrane of the middle ear and mastoid cells in 8 patients;

- oral mucosa in 5 patients;
- kidney tissue in 4 patients;
- gastric mucosa in 2 patients;
- colon mucosa in 1 patient;
- laryngeal mucosa in 1 patient;
- tracheal mucosa in 1 patient.

The total follow-up period ranged from 4 weeks (minimum) to 30 years (maximum). The examination of patients was carried out according to the plan adopted in the clinic, and included the study of anamnesis and physical examination. When familiarizing with the anamnesis, special attention was paid to the presence of relapses of the disease, their number, factors provoking these relapses. The previous therapy of the disease was thoroughly studied, and the total dose of cytostatics received for the entire period of treatment was calculated. Particular attention was paid to the presence of complications of both the disease itself and the therapy.

Instrumental examination included electrocardiography, radiography and computed tomography of the chest organs, ultrasound examination of the abdominal cavity organs, rhinoscopy, X-ray examination and computed tomography of the PNS, esophagogastroduodenoscopy, computed tomography of the skull, larynx and trachea.

When analyzing the course of the disease, localized (damage to the upper respiratory tract, the organ of vision and hearing) and generalized (damage to the upper respiratory tract, the organ of vision and hearing in combination with damage to the lungs and / or kidneys, as well as the gastrointestinal tract, 30 the nervous system, skin) GPU options. Generalized GPA included early systemic, generalized and severe variants of the disease, which are isolated in accordance with the EUVAS classification [12]. GPA relapses were divided into major and minor [15]. Relapses of the disease were considered large, which posed a threat to the patient's life or to the function of a vital organ and required an increase in the glucocorticosteroid (GCS) dose and the appointment of cyclophosphamide, small - a non-life-threatening increase in GPA activity, in which the dose of GCS and / or cytostatic was usually increased.

Statistical analysis. The results were statistically processed using the SPSS for Windows, 22.0 program. (SPSS Inc., Chicago, IL, USA). Quantitative variables were compared using Student's t test and Mann-Whitney test, qualitative ones - using Fisher's exact method. Survival was analyzed using the Kaplan-Meier method. The difference was considered statistically significant at $p < 0.05$.

Results The study involved 60 patients (29 men and 31 women) aged 18 to 80 years with an established diagnosis of GPA. The average age of the examined patients was 48.9 ± 15.6 years. The diagnosis of HPA (n = 60) was established in accordance with the nomenclature adopted in 2012 at the conference in Chapel Hill (USA), as well as on the basis of the presence of at least 2 of 4 criteria of the American College of Rheumatology (ACR), 1990. [7] To confirm the diagnosis of GPA, a biopsy was performed in 40 (66.7%) patients: nasal mucosa or paranasal sinuses - in 17 (28.3%) patients, laryngeal formation - in 5 (8.3%) patients, orbital biopsy - in 12 (20.0%), skin - in 1 (2.3%), tympanic cavity - in 1 (2.3%), lungs - in 1

(2.3%), bronchi - in 1 (2.3%), conjunctiva - in 1 (2.3%). The average period from the onset of the disease to the diagnosis and initiation of treatment was 18.3 ± 32.32 months. At the time of the survey, the average duration of GPA in years was 5.7 ± 4.8 (in months 69.6 ± 57.7). 22 out of 60 patients had a local form of HPA (damage to the upper respiratory tract, the organ of hearing and vision). The local form was diagnosed in 7 men and 15 women aged 18 to 70 years (median age 47.5 years).

In 38 patients, the generalized form of GPA was determined. In 14 men and 24 women aged 22 to 80 years (median age 52.5 years), damage to the upper respiratory tract, the organ of vision, hearing in combination with damage to the lungs and / or kidneys was revealed. In 22 (57.9%) of 38 patients with generalized HPA, a local form of the disease was determined at the onset of the disease. The average time for the development of the generalized form in these patients was 11.7 ± 18.4 months.

Using the BVAS scale, all 60 patients were assessed for exacerbation or remission of the disease. The average BVAS was 2.7 points. The minimum value is 0 points, the maximum is 18 points.

In 32 patients (11 men and 21 women) aged 25 to 80 years, 2 or more points on the BVAS scale were determined, which was regarded as an exacerbation of the disease. The average age of this group of patients was

50.84 ± 14.07 years, median age - 51.5 years. GPA remission was diagnosed in 28 patients (10 men and 18 women) aged 18 to 77 years. The average age in this group of patients is 46.71 ± 17.27 years, the median for age is 49.5 years. The average VDI index was 11.35 ± 5.06. In 46 (76.7%) patients with GPA, ANCA was detected, and in 36 (60.0%) patients ANCA to proteinosis 3 was detected, and in 10 (16.7%) - ANCA to myeloperoxidase.

Of the 60 examined patients with GPA, the most frequently determined lesions of the nose and paranasal sinuses. More than half of the examined patients had lung damage (58.3%), 46.7% of patients with GPA had kidney damage within the framework of vasculitis. The incidence of organ damage in patients with GPA is presented in tab. 2.

Table 2.

The incidence of organ damage in patients with GPA

Clinical features	**N %**
Damage of the nose and PNS	57 (95.0%)
Damage to the organ of hearing	29 (48.3%)
Damage to the organ of vision	33 (55.0%)
Laryngeal lesion	16 (26.7%)
Lung damage	35 (58.3%)
Kidney damage	28 (46.7%)

The defeat of the nose and PNS. The incidence of damage to the nose and PNS in the examined patients was 95.0% (n = 57). The most common cases were ulcerative necrotizing rhinitis (n = 49), lesions of the par PNS in the form of thickening of the sinus mucosa (n = 41), less often - perforation of the nasal septum (n = 30) and destructive sinusitis (n = 36).

Lung damage. Lung involvement was detected in 35 (58.3%) patients with GPA. Most often, radiography or computed tomography of the lungs revealed infiltrates (n = 35), less often - cavities in the lungs (n = 6). One patient (1.7%) with GPA was diagnosed with hemorrhagic alveolitis.

Kidney damage. Kidney damage was detected in 46.7% of patients with GPA (n = 28). Of 28 patients with HPA with kidney damage within the framework of vasculitis, in 19 (31.67%) patients, the glomerular filtration rate was reduced by more than 50% (mean creatinine value 2.16 ± 1.55 mg / dL, mean GFR 35, 8 ± 14.9 ml / min / 1.73 m2). Of 28 patients with kidney damage, 18 (30.0%) people had proteinuria, while proteinuria more than 0.5 g / day was detected in 10 (16.7%) patients, hematuria - in 12 (20.0%) sick. Kidney biopsy was not performed in the examined patients.

Damage to the organ of vision: Most often in the examined patients with GPA, granulomatous lesions of the orbit were determined - (n = 15). 10 (16.7%) patients with GPA developed uveitis, 3 (5.0%) - episcleritis, which were stopped by immunosuppressive therapy and therefore were regarded as a manifestation of the underlying disease.

Damage to the organ of hearing: Most often, damage to the organ of hearing in patients with HPA was associated with the presence of unilateral or bilateral hearing loss (n = 16). Chronic otitis media was detected in 21.7% of cases (n = 13). Granulomatous damage to the mastoid process (mastoiditis) was observed in 9 (15.0%) of the examined patients.

Joint damage: In 8 (13.3%) patients with GPA, joint damage manifested by arthralgia was observed.

Damage to the nervous system: Multiple mononeuritis was diagnosed in 4 (6.7%) patients with gpanulomatosis with polyangiitis.

Skin lesions: It was detected in 5 (8.3%) patients with HPA and manifested itself as vascular purpura.

Damage to the cardiovascular system. Heart damage was observed in 24 (40.0%) patients with GPA. In 22 (36.7%) patients, according to ECHO-KG, atherosclerotic changes of the aortic valve were determined. Cardiomyopathy and chronic heart failure were detected in 2 (3.3%) patients with GPA. Pericarditis was diagnosed in 3 (5.0%) patients.

In all patients, the presence of clinical equivalents of vasculitis and granulomatous inflammation was determined. Signs of vasculitis were detected in 34 (56.7%) patients, signs of granulomatous inflammation - in 45 (75.0%) patients. (Tab. 3)

Table 3.

The incidence of signs of vasculitis and granulomatous inflammation in patients with GPA.

1. Signs of vasculitis	34 (56.7%)
Glomerulonephritis	28 (46.7%)
Hematuria or hematuria combined with proteinuria	28 (46.7%)

Extrarenal vasculitis	12 (20.0%)
Cutaneous vasculitis	5 (8.3%)
Episclerite	3 (5.0%)
Multiple mononeuritis	4 (6.67%)
2. Signs of granulomatous inflammation	45 (75.0%)
Granulomatous inflammation on biopsy	40 (66.7%)
Lung infiltrates / nodes: persistent (more than 1 month) with disintegration, cavity formation and / or stenosing endobronchitis	35 (58.3%)
Damage to the ENT organs or eyes:	
Perforation of the nasal septum	30 (50.0%)
Destructive sinusitis	37 (61.7%)
Sublining stenosis of the larynx or trachea	16 (26.7%)
Orbital pseudotumor	15 (25.0%)
Polypoid thickening of the mucous membrane of the paranasal sinuses (lasting at least 3 months)	42 (70.0%)
Mastoiditis (lasting at least 3 months)	9 (15.0%)

12 (20.0%) patients with GPA with extrarenal manifestations of vasculitis (cutaneous vasculitis, episcleritis, mononeuritis), 7 (11.6%) patients were found to have a combination of extrarenal manifestations of vasculitis with kidney damage within the framework of GPA. In 5 (8.3%) patients with GPA, there were no data for kidney damage: (2 (3.3%) patients had a local form of GPA, 3 (5.0%) patients had a generalized GPA head start with lung damage.

The frequency of organ damage, the development of signs of granulomatous inflammation and vasculitis, depending on the presence of exacerbation or remission of the disease, local or generalized form of HPA, is presented in tab. 4.

Table 4.

Organ damage, the presence of signs of granulomatous inflammation and vasculitis in patients with various forms and periods of the disease

	Form of disease		Disease period	
	Local (n = 22)	General (n = 38)	Aggravation (n = 32)	Remission (n = 28)
VDI	7,27±2,62	13,71±4,68	12,13±5,28	10,46±4,82
Damage of the organ of vision	12 (54.5%)	21 (55.3%)	13 (40.62%)	20 (71.4%)
Damage to the organ of hearing	8 (36.4%)	21 (55.3%)	12 (37.5%)	17 (60.7%)

Damage to the nose, paranasal sinuses	20 (90.9%)	37 (97.4%)	32 (100.0%)	25 (89.3%)
Laryngeal lesion	7 (31.8%)	9 (23.7%)	8 (25.0%)	8 (28.6%)
Lung damage	0	35 (92.1%)	22 (68.8%)	13 (46.4%)
Kidney damage	0	28 (73.7%)	14 (43.8%)	14(50.0)
Signs of vasculitis	3 (13.6%)	31 (81.5%)	19 (59.4%)	15 (53.6%)
Signs granulomatous inflammation	19 (86.4%)	26 (68.4%)	29 (90.6%)	16 (57.1%)

In patients with exacerbation of GPA, compared with patients, in remission of GPA, the most frequent increase in the content of ESR and C-reactive protein. The main laboratory parameters are presented in table 5.

Table 5.

Laboratory indicators in patients with GPA, depending on the form and the period of the disease

	General	Form of the disease		Disease period	
	N = 60	Local (n = 22)	Generalized (n = 38)	Aggravation (n = 32)	Remission (n = 28)
Speed glomerular filtration less 60 ml / min / 1.73 m2	19 (31.7%)	0	19 (50.0%)	11 (34.4%)	8 (28.6%)
Proteinuria	18 (%)	0	18 (47.4%)	9 (28.%)	9 (28.1%)
Proteinuria more than 0.5 g / day	10 (16.7%)	0	10 (26.3%)	6 (18.8%)	4 (14.3%)
Level up blood creatinine	16 (26.7%)	0	16 (42.1%)	10 (31.3%)	6 (10.0%)
Mean creatinine, mg / dl	1.29±1.1	0.91±0.2	1.5±1.3	1.48±1.4	1.08±0.4
GFR calc. CKDEPI, ml / min	67.3±28.3	80.1±19.9	59.9±28.2	62.5±28.1	72.7±28.0
Hematuria	12 (20.0%)	0	12 (31.6%)	8 (25.0%)	4 (14.3%)
Mean daily proteinuria, g / day	0.21±0.6	0.03±0.1	0.32±0.7	0.26±0.7	0.16±0.3
Increased ESR	29 (48.3%)	7 (31.8%)	22 (57.9%)	20 (62.5%)	9 (32.1%)
Mean ESR, mm / h	18.02±16.8	12.23±7.3	21.37±19.8	23.69±20.6	11.54±7.1
Increased CRP	13 (21.67%)	2 (9.1%)	11 (28.9%)	12 (37.5%)	1 (3.6%)

A decrease in the glomerular filtration rate by more than 50% was diagnosed in 19 (31.67%) patients with GPA with renal vasculitis. In 1 (1.7%) patient, the development of RPGN was noted (an increase in creatinine from 5 mg / dL to 8.3 mg / dL). Urinary syndrome in patients with GPA was mainly manifested by hematuria and proteinuria (PU up to 1 g / day in 16 (89.5%), 1-3 g / day - 1 (5.3%), more than 3

g / day (nephrotic syndrome) - 1 (5.3%), which were more common in patients with exacerbation of HPA.

Discussion The results of the study showed that the clinical manifestations of GPA have not changed significantly over the past 40 years, however, the survival rate of patients has increased significantly. The disease developed more often in women around the age of 40, although in the prospective cohort there was a significant increase (up to 12.5%) in the proportion of patients who were diagnosed in old age. In 2/3 of patients, the first manifestations of HPA included damage to the upper respiratory tract (nasal discharge, crusting, etc.) and general symptoms (fever, malaise, joint pain). In recent years, we have noted an increase in the proportion of patients with a local variant of HPA (from 24.6% to 32.0%), which probably reflects an increased awareness of this disease among otorhinolaryngols and ophthalmologists. It should be noted that the classification of HPA, proposed by EUVAS, involves the identification of 5 variants of the disease - local, early systemic, generalized, severe and refractory to treatment [16,17,24]. We used a simplified classification and combined the early systemic, generalized, and severe forms of HPA into a "generalized" version of the HPA. This approach has increased the statistical power of the analysis. In addition, any visceral manifestations of GPA are unfavorable. Damage to the kidneys and lungs was observed in more than half of the patients with GPA. In the prospective cohort, the incidence of visceral manifestations 56 decreased slightly, but the difference between the two cohorts did not reach statistical significance. Kidney damage in most cases was manifested by mild proteinuria and / or microhematuria. More severe variants of kidney damage (nephritic and nephrotic syndromes, rapidly progressing nephritis, acute kidney damage) were much less common, but about 20% of patients experienced the development of chronic renal failure, including those requiring renal replacement therapy (hemodialysis or kidney transplantation). The main variants of lung damage were lung infiltrates, complicated by the formation of decay cavities, and alveolar bleeding, which developed with widespread infiltrative changes in the lungs. Lung involvement was often life-threatening (the frequency of alveolar bleeding in two cohorts of patients was 19-22%) and was one of the main causes of death. In 5% of patients, fulminant development of hemorrhagic alvolitis and / or rapidly progressive glomerulonephritis was noted within 1-2 months after the onset of the disease.

The relapse rate was quite high in both cohorts, but in the prospective cohort it slightly decreased due to patients with generalized HPA. The data obtained indirectly confirm the effectiveness of more "sparing" immunosuppressive therapy (methotrexate, azathioprine, glucocorticosteroids only), which we have begun to use more often in recent years [18,22].

Conclusions

1. In the retrospective and prospective groups, patients with a generalized variant of HPA prevailed (75.4% and 67.9%, respectively), although the share of a local variant of the disease with isolated lesions of the upper respiratory tract, organs of vision and hearing has statistically significantly increased over the past 10 years. (from 24.6% to 32.1%).

2. The local variant of HPA is characterized by a more favorable course, and for its treatment it is often sufficient to use lower doses of glucocorticosteroids and cytostatics, which are less toxic than cyclophosphamide.

3. Among the manifestations of the visceral variant of HPA, the central place in frequency is occupied by damage to the lungs (52.3%) and kidneys (50.8%), while damage to the gastrointestinal tract (29.7%) and the nervous system (32, 0%) is much less common.

4. Lung damage occurs early (after 2.5 ± 2.3 months from the onset of general and / or local symptoms), manifests itself as infiltrates with a tendency to rapid disintegration and alveolar bleeding, but may have an asymptomatic course.

5. For the diagnosis of exacerbation (activity) of HPA, an increase in the level of ANCA in the blood serum and a decrease in the index of endothelium-dependent vasodilation are important (sensitivity - 71.4% and 85.7%, respectively; specificity - 85.7% and 78.6%), and for the differential diagnosis of exacerbation of HPA from infectious complications, the procalcitonin test can be used (sensitivity - 57.1%; specificity - 71.4%).

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