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GOODPASTURE SYNDROME: CASE REPORT*

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У роботі наведені сучасні дані зарубіжної літератури, які стосуються синдрому Гудпасчера – імунно-запальної патології, що характеризується утворенням аутоантитіл до базальних мембран ниркових клубочків і легеневих альвеол, і виявляється геморагічним пневмонітом в поєднанні з легеневою кровотечею (кровохарканням) та гломерулонефритом. Етіологічні механізми захворювання достовірно не визначені. Клінічні спостереження вказують на зв'язок розвитку синдрому Гудпасчера з перенесеною вірусною інфекцією, прийомом лікарських препаратів, виробничою шкодою. Частота розвитку синдрому Гудпасчера становить 1 випадок на 1 млн. населення. У зв'язку з рідкістю даної патології кожен випадок синдрому Гудпасчера представляє великий теоретичний і практичний інтерес. Проведений аналіз власного клініко-морфологічного випадку синдрому Гудпасчера. При проведенні патологоанатомічного дослідження тіла померлого виявлені морфологічні ознаки, що свідчать про наявність при житті синдрому Гудпасчера, основними проявами якого слід вважати геморагічний пневмоніт і мезангіопроліферативний гломерулонефрит з подальшою фібропластичною трансформацією клубочків. В даному випадку безпосередньою причиною смерті слід вважати гостру легенево-серцеву недостатність, так як патоморфологічні зміни в легенях превалювали над такими в нирках, що повністю відповідає клінічній картині та результатам лабораторних досліджень. Певний інтерес даний випадок представляє також в сенсі грамотного формулювання остаточного діагнозу, так як можна говорити про поєднання двох захворювань: синдрому Гудпасчера і гострого флегмонозного апендициту з місцевим перитонітом. Постановка діагнозу синдрому Гудпасчера в клініці не завжди буває своєчасним, свідчить про важкий стан пацієнта, вимагає ретельної диференціальної діагностики з рядом інших захворювань, що супроводжуються геморагічним легенево-нирковим синдромом, і потребує невідкладного призначення активної терапії імуносупресорами, включаючи преднізолон і цитостатики. Вчасно розпочате адекватне лікування значно покращує прогноз пацієнтів.

Ключові слова: синдром Гудпасчера, гломерулонефрит, геморагічний пневмоніт, флегмонозний апендицит, легенева кровотеча.

The Goodpasture syndrome is an immune-inflammatory pathology characterized by the formation of autoantibodies directed against the basement membranes of the renal glomeruli and pulmonary alveoli, manifested by hemorrhagic pneumonitis in combination with pulmonary hemorrhage (hemoptysis) and glomerulonephritis. To date, etiological mechanisms of the disease are unknown. Clinical observations indicate a relationship between the development of Goodpasture syndrome and viral infection, intake of medications, industrial hazards. The incidence of Goodpasture syndrome is estimated to be 1 case per 1 million population. Due to the rarity of this pathology, each case of Goodpasture syndrome is of great theoretical and practical interest. The authors conducted the analysis of clinical and morphological observation of Goodpasture syndrome. The postmortem study revealed morphological signs indicating the presence of Goodpasture syndrome inter vivos, whose main manifestations were hemorrhagic pneumonitis and mesangial-proliferative glomerulonephritis with fibroplastic transformation. The reported case is also of particular interest in terms of correct formulation of the final diagnosis, since there was a combination of two diseases: Goodpasture syndrome and phlegmonous appendicitis with focal peritonitis. In this case, pulmonary heart failure should be considered as the direct cause of death, since pulmonary lesions prevailed over the renal ones, which is fully consistent with the clinical presentation and findings of the laboratory tests. The diagnosis of Goodpasture syndrome made at the hospital is not always timely, as can be evidenced by patient's severe condition, and it requires careful differentiation with a number of other diseases involving hemorrhagic pulmonary and renal syndrome, and the urgent need for active therapy with immunosuppressants, including prednisone and cytostatics. The timely adequate treatment significantly improves the prognosis.

Keywords: Goodpasture syndrome, glomerulonephritis, hemorrhagic pneumonitis, phlegmonous appendicitis, pulmonary hemorrhage..

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Goodpasture syndrome (GPS) is an immune-inflammatory pathology characterized by the formation of autoantibodies directed against the basement membranes of the renal glomeruli and pulmonary alveoli, manifested by hemorrhagic pneumonitis in combination with pulmonary hemorrhage (hemoptysis) and glomerulonephritis [2, 3].

The disease was first described by an American physician and pathophysiologist E.W. Goodpasture (1886–1960) during the influenza epidemic in 1919 in the 18-year-old young man who developed kidney damage in the form of nephritis and pneumonia, followed by hemoptysis within one month after suffering flu [8]. The incidence of Goodpasture syndrome is estimated to be 1 case per 1 million population. There are two age peaks of incidence: at the age of 20-30 years and 50-60 years; it occurs more commonly in males [5, 9]. If untreated, mortality among patients reaches 75–90% [17]. Due to the rarity of this pathology, each case of Goodpasture syndrome is of great theoretical and practical interest. [5, 9].

Etiological mechanisms of the disease are unknown. Clinical observations indicate a relationship between the development of Goodpasture syndrome and viral infection (influenza, Viral Hepatitis A, etc.), intake of medications (carbimazole, penicillamine), industrial hazards (inhalation of organic solvent vapors, varnishes, gasoline), hypothermia, smoking [4]. Genetic susceptibility to this syndrome has been noted in individuals-carriers of HLA-DRwl5, HLA-DR4 and HLA-DRB1 alleles. Family cases of Goodpasture syndrome have been also described.

Under the influence of one or another etiological factor, as a result of changes in the tolerance of the immune system, the body begins to produce autoantibodies directed against the basement membranes of the pulmonary alveoli and the renal glomeruli [6]. It is hypothesized that the structural component (NC-1) a-3 of type IV collagen chains, which is present in the basement membranes of the pulmonary and renal capillaries, plays the role of an autoantigen. Formed antibodies against the components of the basement membranes of the alveoli and renal glomeruli (anti-GBM antibodies) in the presence of C3-complement bind to antigens; the resulting immune complexes are deposited along the basement membranes, inducing immuno-inflammatory damage to the renal glomeruli (glomerulonephritis) and pulmonary alveoli (alveolitis) [7, 9, 11]. In the development of autoimmune inflammation, activation of cellular elements (T-lymphocytes, endotheliocytes, monocytes, alveolar macrophages, polymorphonuclear leukocytes), cytokines (insulin-like, platelet growth factors, tumor necrosis factors, interleukin-1), free radicals, proteolytic enzymes, adhesive molecules and other factors damaging renal tissue, play a significant role [10]. In the development of alveolitis in Goodpasture syndrome, activation of alveolar macrophages is of great importance. In the activated state, they release about 40 cytokines. Type I cytokines (chemotaxins, leukotrienes, interleukin-8) enhance the entry of polymorphonuclear leukocytes into the lungs. Type II cytokines (platelet, macrophage growth factors) promote transfer of fibroblasts into the lungs. Alveolar macrophages also produce reactive oxygen species, proteases, that damage pulmonary tissue.

The pathomorphological manifestations of Goodpasture syndrome are hemorrhagic necrotizing alveolitis and nephrosonephritis. Histological study of renal tissue reveals proliferative-membranous, proliferative or necrotizing glomerulonephritis, glomerular sclerosis, and renal parenchyma fibrosis. Morphological study of pulmonary tissue reveals capillary disease with pronounced destruction and proliferation phenomena of predominantly interalveolar septa, alveolitis with hemorrhagic exudate into the alveoli, pulmonary infiltrates, hemosiderosis, pneumosclerosis [1].

Three variants of the clinical course of the Goodpasture syndrome are distinguished: malignant (which is characterized by recurrent hemorrhagic pneumonia and rapidly progressive glomerulonephritis), moderate (with a slower development of lesions in the kidneys and lungs) and slow (with prevailing phenomena of glomerulonephritis and chronic renal failure and late development of pulmonary manifestations) [17].

The most sensitive and specific method for diagnosing Goodpasture syndrome is the determination of serum antibodies against glomerular basement membrane (Anti-GBM) by indirect immunofluorescence technique or, if available, enzyme-linked immunosorbent assay (ELISA) with recombinant or human NC-1α-3 (in the highest concentrations it is found in the basement membranes of the renal and pulmonary capillaries). The presence of these antibodies confirms the diagnosis [12]. In case when anti-GBM antibodies are not detected, though symptoms of glomerulonephritis (hematuria, proteinuria, urinary red blood cells casts, kidney failure, or a combination of these symptoms) are present, a kidney biopsy is indicated to confirm the diagnosis. Immunofluorescence staining of the renal or pulmonary tissue classically detects linear deposition of IgG along glomerular or alveolar capillaries [16]. Similar changes can also occur in diabetic nephropathy and fibrillar glomerulonephritis, a rare disease causing pulmonary-renal syndrome, but the fixation of antibodies to the glomerular basement membrane in these diseases is nonspecific and does not occur linearly.

The clinical course of Goodpasture syndrome is steadily progressive; the prognosis is unfavorable. Generally, patients die due to massive pulmonary hemorrhages, severe renal or pulmonary failure. It is believed that high levels of serum creatinine, oligoanuria, the absence of normal glomeruli and a high percentage of demilunes in the kidney biopsy, and the circulation of antibodies to the glomerular basement membrane in high titre determine the severity of the clinical course of the disease [15]. The survival rate of patients from the onset of the disease varies from a few months to 1-3 years.

We report a lethal case of GPS combined with the acute appendicitis and subsequent postmortem verification.

The 22-year old patient L. was referred to Nephrology Unit at the Regional Clinical Hospital from the Central District Hospital.

It is known from the history that the patient suffered from edema of lower extremities, headache and elevated blood pressure (160/90 mmHg) during the last five months. During the last month, he complained of worsening of the general state of health and was admitted to the Therapeutic Unit at the Central District Hospital in the place of residence. The patient was examined clinically, laboratory and instrumentally. Complete blood count showed: WBC $7{,}5x10^9$/L L 7.5x109 / l, RBC $3{,}4x10^{12}$/L, hemoglobin 106 g / L, ESR 19 mm/h, eosin. 0%, stab7%, segment.80%, lymphocytes 11%, monocytes 2%. Urinalyses showed: protein 1.47 g/l, WBCs 4-5 per power field, RBCs 25-30 per power field. Biochemical blood test showed: total bilirubin 14.7 μmol/L, direct bilirubin 4.2

μmol/L, indirect bilirubin 10.5 μmol/ L, urea 14.7 mmol/L, creatinine 293 μmol/L, total protein 59 g/L, prothrombin index 86%, fibrinogen 3.55 g/L.

Based on the resulting data, the diagnosis was made: the acute glomerulonephritis with stage 2 acute renal failure. Mild anemia. Stage 2 arterial hypertension of the second degree, risk II. Uremic pneumonitis is uncertain. Right kidney cyst.

Within 3 days in a state of moderate severity, with complaints of severe general weakness, shortness of breath, dizziness with changes of body posture, nausea, edema of lower extremities, elevated blood pressure to 200/100 mm Hg the patient was transferred to the Nephrology Unit at the Regional Clinical Hospital to clarify the diagnosis and follow-up treatment.

On the fifth day of the in-patient treatment, the patient suddenly complained of severe pain in the right inguinal region, and after consultation with a surgeon, a diagnosis was made: acute appendicitis, which was followed by appendectomy, with subsequent sanation and drainage of the abdominal cavity.

After surgery, the patient's condition remained severe; there were complaints of general weakness, dizziness, hemoptysis. Chest CT revealed signs of bilateral infiltration of the lung tissue, bilateral hydrothorax, and lymphadenopathy.

Based on clinical, laboratory and instrumental findings (hemoptysis, shortness of breath, symptoms characteristic of glomerular lesions of the kidneys, uremia, chest X-ray and CT), a clinical diagnosis was made: glomerulonephritis, urinary syndrome, severe course, CRF III. Arterial hypertension stage II, grade 3, high risk. Goodpasture syndrome (alveolitis, pulmonary hemorrhage). Secondary hypochromic and severe post-hemorrhagic anemia. Acute phlegmonous appendicitis, local serous peritonitis.

Despite continued therapeutic medical care, the patient's condition rapidly deteriorated due to progressive cardiovascular insufficiency and on day 2 thereafter the patient died.

The autopsy revealed morphological signs indicating the presence of GPS *inter vivos*, the main manifestations were hemorrhagic pneumonitis and mesangial-proliferative glomerulonephritis with fibroplastic transformation.

Thus, the lungs, while maintaining normal size, were diffusely compacted in all parts, dark red on the surface and in the section (Fig. 1).

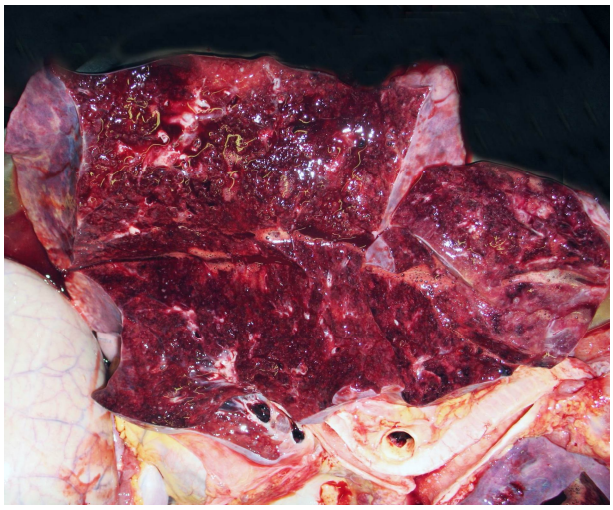

Fig.1 Macroscopic view of the left lung.

Microscopic study revealed that in the lung tissue of its almost all parts, the alveoli were filled with blood, with the presence of hemolyzed erythrocytes, focal aggregations of hemosiderophages. This fact gives evidence of old long-term intra-alveolar hemorrhages. In some places in the alveoli hydropic fluid was found, the interalveolar septa were markedly thickened with blood microvessels with thickened and loosened walls, proliferation of the endothelium (Fig. 2).

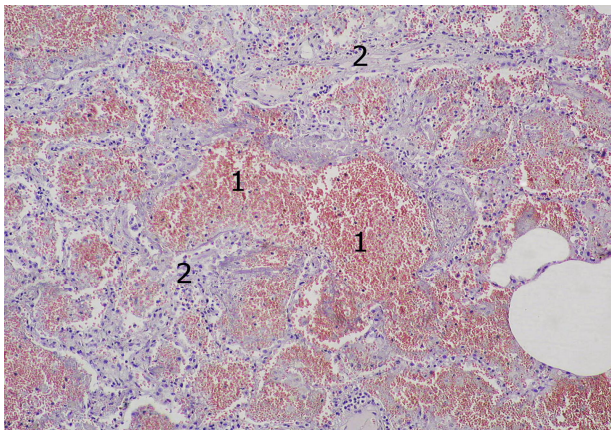

Fig .2 Microscopic view of the lung
H&E stain,150× magnification.
1 – alveoli filled with blood, 2 – thickened interalveolar septa.

Dimensions of the kidneys did not have significant deviations from the norm and were: right kidney : 11x6x5 cm, left kidney: 11x5.5x4.5 cm. The surface of the kidneys was smooth, pale brown, with multiple red dots. On the section the tissue was rather dense, pale brown, the layers were not clearly differentiated. The cortex was colored pale brown with multiple red dots; the renal pyramids were pink-brown. The pelves and calyces were not dilated, filled with a yellowish transparent fluid; their mucous membrane was pale gray and smooth.

Microscopic study of the kidneys showed that most of the capillary glomeruli were enlarged with significant increase in the number of cellular elements, mainly due to mesangiocytes, depletion and narrowing of the capillary lumen; the glomerular capsules were markedly thickened (Fig. 3).

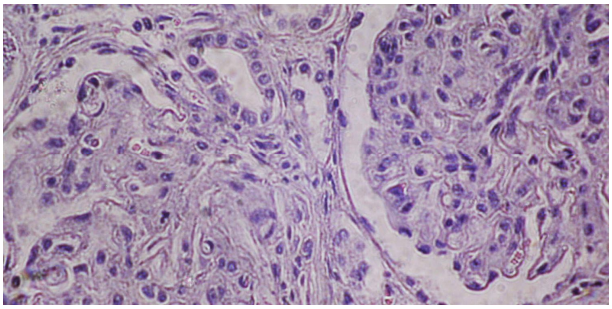

Fig.3 Microscopic view of the lung
. H&E stain, 600× magnification.

At the same time, in both kidneys, glomeruli with varying degrees of fibroblastic transformation were constantly noted, the initial stages of which were manifested by the moderate atrophy and sclerosis, and terminal ones with hyalinosis. In the renal interstitium a diffuse and small-focal inflammatory infiltration was detected, represented mainly by lymphocytes and plasma cells. Heterogeneous blood filling was characteristic for blood vessels (Fig. 4).

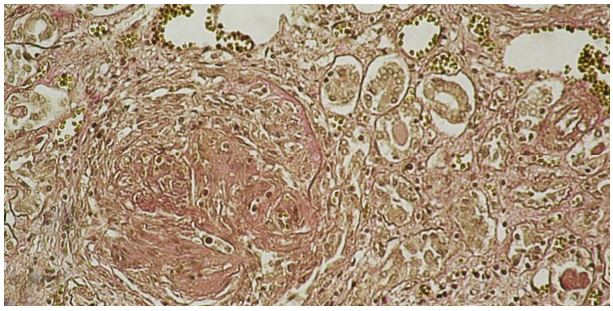

Fig.4 Microscopic view of the lung.
Van-Gieson stain, 400 × magnification.

Capillary glomeruli with varying degrees of fibroblastic transformation, in the interstitium - diffuse inflammatory infiltration.

In the epithelial cells of the renal tubules, lesions, characteristic of hydropic dystrophy, were noted; sometimes we observed the development of total necrosis, as evidenced by the destroyed and partially lysed nuclei of nephrocytes.

In the other internal organs, nonspecific changes characteristic of intoxication and progressive pulmonary heart failure were detected.

On the basis of the combination of the lesions listed above, the final combined (bi-causal) postmortem diagnosis was made: *Underlying diseases*: 1. Goodpasture syndrome, mesangial-proliferative glomerulonephritis, hemorrhagic pneumonitis. 2 Phlegmonous appendicitis with local serous peritonitis. Surgery: appendectomy, drainage of the abdominal cavity. *Complications of the underlying diseases*: Hydrothorax: 500 ml on the left, 300 ml on the right. Anemia, parenchymal dystrophy of internal organs, focal pulmonary edema, brain edema.

This case is also of particular interest in terms of correct formulation of the final diagnosis, since it was noted above that there was a combination of two diseases: GPS and phlegmonous appendicitis with focal peritonitis. Most likely, in this case, phlegmonous appendicitis, not conjoint with GPS, could not lead to death of the patient, considering the promptly performed surgical intervention without complications. At the same time, it cannot be denied that the presence of phlegmonous appendicitis, the surgery (performed according to vital signs) aggravated the severity of the patient's state of health and accelerated the lethal outcome.

Thus, in the reported case, there are two, mutually complicating (combined) underlying diseases, described in the postmortem diagnosis [13, 14]. In this case, pulmonary heart failure should be considered as the direct cause of death, since pulmonary lesions prevailed over the renal ones, which is fully consistent with the clinical picture and findings of the laboratory tests.

The diagnosis of GPS made at the hospital is not always timely, as can be evidenced by patient's severe condition, and it requires careful differentiation with a number of other diseases involving hemorrhagic pulmonary-renal syndrome, and the urgent need for active therapy with immunosuppressants, including prednisone and cytostatics. Timely adequate treatment significantly improves the prognosis.

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