International Journal of Education, Social Science & Humanities.
Finland Academic Research Science Publishers
ISSN: 2945-4492 (online) | (SJIF) = 7.502 Impact factor
Volume-12| Issue-1| 2024 Published: |22-01-2024|

UDC: 616.61-036.12-07-037

CLINICAL CASE OF SECONDARY ANTIPHOSPHOLIPID SYNDROME IN A NEPHROLOGICAL PATIENT

https://doi.org/10.5281/zenodo.10637045

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Summary

The article describes a clinical case of late diagnosis of secondary aPL with multiinflammatory syndrome in a patient with chronic glomerulonephritis. The experience of Covid-19 led to the launch of systemic homeostasiological disorders, which manifested as thrombosis in the inferior vena cava, renal vein, and lower lobe pulmonary artery. In this case, the onset of the disease was "varicocele," which most likely was a manifestation of thrombosis of the spermatic cord vein. The addition of arterial hypertension, anasarca, massive proteinuria with active urinary sediment, hypoproteinemia , hypercreatininemia was regarded as manifestations of clinical and laboratory signs of a mixed form of CGN with impaired renal function, which required pulse therapy with a glucocorticosteroid and a cytostatic in combination with combined nephroprotective therapy against the background of anticoagulants and antiplatelet agents .

Key words

Antiphospholide syndrome, chronic glomerulonephritis, arterial hypertension.

Patient A., 39 years old, was admitted to the nephrology department in May 2023 with a clinically established **diagnosis:** main: chronic glomerulonephritis, mixed form with impaired renal function; competing: thrombosis of the left renal vein; o complication: post-Covid multiinflammatory syndrome, secondary antiphospholipid syndrome (APL) seropositive; background: chronic tonsillitis, toxic-allergic form, condition after thrombosis of the inferior vena cava. Complication: ascites, left-sided hydrothorax.

Upon admission, the patient had the following **complaints:** headache in the frontal, occipital and parietal regions, dizziness, palpitations, shortness of breath on mild physical exertion, a feeling of lack of air, massive swelling throughout the body, scanty excretion of cloudy urine, loss of appetite, general weakness.

History of the disease: ill since January 2023, when he suffered from mild Covid-19, confirmed by ELISA and PCR. took nonsteroidal anti-inflammatory

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drugs (acetylsalicylic acid at a dose of 100 mg/ day for 10 days). 3 days after the end of treatment, the patient developed pain and swelling of the left testicle, and surgery was performed with a diagnosis of varicocele. After 2-3 days, the patient developed severe pain in the left lumbar region, which was not relieved by conventional analgesics; later, massive swelling of the lower extremities and heaviness in them, as well as general weakness, occurred. In early April, according to the results of MSCT of the abdominal cavity, thrombosis of the inferior vena cava and the left renal vein, the lower lobe pulmonary artery on the right, left-sided hydrothorax with collapse of the adjacent lung tissue, encysted pleurisy on the right, moderate ascites were established, and ultrasound of the kidneys showed signs of nephritis. Renal stintigraphy data: kidneys with smooth, clear contours and uneven accumulation of radiopharmaceuticals in them, renographic curves are symmetrical, vascular, secretory and excretory phases of both kidneys are within normal limits, symmetrical, functional parameters and renal plasma cells of both kidneys are normal. A clinical diagnosis was made: chronic glomerulonephritis, nephrotic form. Competing: thrombosis of the left renal vein and inferior vena cava Treatment received (sodium heparin, calcium nadroparin, albumin repeatedly, drainage and evacuation of fluid from the pleural cavity). The treatment received led to a short-term positive result. However, after 5-6 days the swelling increased again. The results of additional studies demonstrated the following deviations from normal values: in the blood - hemoglobin level -102 g/l, creatinine - 112 μmol /l, total protein - 46.9 g/l, albumin -32 g/l. In urine - protein 5.28 ppm, leukocytes - 4-5-5\1, granular casts - 1-0-1\1. Ultrasound: kidneys - signs of nephropathy, liver compaction, liver hemangioma, acalculous cholecystitis, left-sided hydrothorax. Analysis of pleural fluid: protein - 3%, red blood cells - 2-4-3-8 in 1 ml.

The patient received the following treatment: prednisolone 30 mg/ day orally, rivaroxaban 20 mg/ day orally, sodium heparin 5000 units/ day subcutaneously, deproteinized calf blood derivative 5 ml intravenously jet, ketosteril 3 tablets / day, furosemide 1% solution 4.0 ml intravenous jet, torasemide 0.5% solution 4.0 ml intravenous jet, fresh frozen plasma 4 g in saline solution 0.9% 250 ml, levofloxacin 0, 5% 100 ml, puncture of the pleural cavity to evacuate fluid. After discharge from the hospital, the patient abruptly stopped taking prednisone and after 3 days the swelling increased sharply again, and therefore 3 sessions of pulse therapy with glucocorticosteroids 500 mg with sodium heparin 5000 units in 0.9% saline were performed, after which he acne appeared all over the body. To clarify the diagnosis and develop treatment tactics, the patient was hospitalized at the TTA

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multidisciplinary clinic in the nephrology department for examination and treatment.

Anamnesis of life. Among the diseases he has suffered, he notes frequent colds, sore throats, an episode of red urine, acute viral hepatitis A, surgery (varicocele). Denies allergic diseases. Heredity is not burdened. Objectively: the general condition of the patient is of moderate severity, the position is active, the physique is normosthenic . The skin and visible mucous membranes are pale, profuse acne all over the body and under the arms. The subcutaneous fat layer is moderately developed. There is massive swelling on the body (limbs, anterior abdominal wall, scrotum). Peripheral lymph nodes (axillary, inguinal) are not enlarged and painless. Respiratory system: respiratory rate -22 min. The chest is painless on palpation, elasticity is preserved. When percussing the lungs in the lower parts on the right - shortening of the percussion sound, on the left in the lower parts percussion - a dull sound, auscultation - weakened vesicular breathing on both sides, in the lower part of the left lung, starting from the 5th rib, breathing is not heard. Cardiovascular system: upon percussion, the borders of the heart: expanded to the left (along the left midclavicular line in V intercostal space). On auscultation, heart sounds are moderately muffled and rhythmic. Pulse – 98 min., blood pressure 150/90mmHg. Art. Digestive system: the tongue is moist, coated with a light grayish coating. The abdomen is significantly increased in volume due to ascites; palpation is soft and painless. The liver is at the edge of the costal arch the spleen is not enlarged. The chair is regular and formed. Genitourinary system. The amount of daily urine is significantly reduced (about 700 ml/ day), cloudy. Endocrine and nervous systems: no complaints, the thyroid gland is not enlarged, painless on palpation, pathological symptoms, paresis and paralysis are absent.

Laboratory indicators in the dynamics of treatment

Index	**Norm**	**before treatment**	**on the 7th day of treatment**
Hemoglobin	130-160 g/l	118	117
Red blood cells	4.0-5.0 10 x12 g/l	3.7	3.7
CPU	0.85-1.05	0.8	0.8
Leukocytes	4-9x10x3/l	9.0	13.4
Platelets	180-320 103/l	228.0	228.0
S/B	47-72%	72	74
Eosinophils	0.5-5.0%	6	6
Lymphocytes		15	12
ESR	2-10 mm/h	19	15
VSK	3-5 min	N-3.37. K-4.14	N-3.34. K-4.27

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Urea	1.7-8.3m/mol	8.5	7.8
Creatinine	44-115 'μ\mol	140.5	110.0
Albumen	35-50g/l	18.6	28.4
Total protein	65-85 g/l	35.9	38.2
Fibrinogen	2-4 g/l	7.43	6.75
INR	up to 1.0	1.20	1.36
Urinalysis according to Nechiporenko	in 1 ml of urine leukocytes 4000 red blood cells -1000 cylinders –up to 24	leukocytes 15500 erythrocytes 13750 hyaline cylinders-16	leukocytes 11000 erythrocytes 18000 hyaline cylinders 24-36
General urine analysis	protein – abs leukocytes -0-1-3 red blood cells -0-0-1 cylinders - abs	protein 9.9 leukocytes:13-16-18 /1 red blood cells: variable --20-24/1 unchanged -8-10/1 cylinders: hyaline-4-6/1 granular–13-15-19/1 waxy -5-6/1	protein 9.9 leukocytes: 5-6 /1 red blood cells: unchanged-7-8-10/1 Cylinders: hyaline -2-4/1 granular–3-6 8-/1
Lupus anticoagulant (LA1)	31-44 sec	58.7	
Lupus anticoagulant (LA2)	30-38 sec	41.1	
Anticoagulant ratio (LA1/LA2)	neg < 1, 2	1.4	
IgG antibodies to cardiolipin	0-10 U / ml	18.6	
IgM antibodies to cardiolipin	0 - 7 U / ml	22.6	
IgG antibodies to beta-2-glycoprotein	<10 U / ml	13.4	
ATgM to beta-2-glycoprotein	<10 U / ml	12.7	

ECG: Sinus rhythm, heart rate 85/min. The EOS is shifted to the left, diffuse metabolic changes in the myocardium. Ultrasound of the abdominal cavity and kidneys (conclusion): echo signs of moderate hepatomegaly with increased exogeneity, angiomas of the right lobe, signs of chronic cholecystitis, chronic

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nephritis, ascites, left-sided hydrothorax. Chest X-ray - left sided Hydthorax. The patient categorically refused a kidney biopsy. The patient in the hospital received the following treatment: methylprednisolone 1.0 g in 200 ml of 0.9% saline with sodium heparin 5000 units on days 1 and 3, on days 2 - in combination with 1000 mg of cyclophosphamide, pentoxifylline 2% solution 5 ml on 200 ml of 0.9% saline, pentoxifylline 600 mg/ day. orally, sodium heparin 5000 units/ day. subcutaneously, L -arginine aspartate 4.2% 100 ml, ovomine 60,000 ATE (5 ml) intravenous drip of 200 ml of 0.9% saline, tocopherol acetate 400 mg/ day. orally, amoxicillin 875 mg + clavulanic acid 125 mg, 1 tablet 2 times a day, omeprazole 40 mg/ day. orally, furosemide 1% solution 4.0 ml intravenously, potassium aspartate and magnesium aspartate 1 tablet 3 times a day, torasemide 0.5% solution 4.0 ml intravenously, rheopolyglucin 10% solution 200 ml intravenously. After treatment, the patient's condition improved somewhat, headaches, dizziness and palpitations disappeared, he sometimes noted heaviness in the head and slight shortness of breath when walking, swelling decreased significantly, urine output increased significantly (up to 2800-3200 ml/ day), and appetite appeared. The patient was discharged for outpatient treatment under the supervision of a nephrologist with recommendations for a sharp restriction of sodium chloride to 3 g/ day, spicy food, daily intake of methylprednisolone 48 mg/ day according to the schedule, cyclosporine 200 mg/ day, pentoxifylline 600 mg/ day, tocopherol acetate 400 mg/ day, ascorbic acid 50 mg + rutoside 50 mg, 2 tablets. 3 times a day. A kidney biopsy is recommended to confirm the diagnosis.

This case is of clinical interest due to the delayed diagnosis of secondary aPL with systemic thrombosis in a patient with chronic, most likely post-streptococcal glomerulonephritis (history of frequent sore throats). In this case, the trigger for multisystem microcirculatory disorders was Covid-19, and the debut of these clinical manifestations was thrombosis of the inferior vena cava and, most likely, thrombosis of the vein of the spermatic cord, which is what happened in this patient. As is known, with thrombosis of the inferior vena cava there is a real danger of thrombosis in the pulmonary artery system, which was observed in this case. However, evidence of a cascade of thrombosis appeared only in an MSCT study, which was carried out for severe pain in the left lumbar region, which was not relieved by analgesics and the appearance of massive swelling of the legs. We regarded the development of moderate arterial hypertension, anasarca, massive proteinuria with active urinary sediment, hypoproteinemia, increased creatinine and urea levels as manifestations of clinical and laboratory signs of a mixed form of CGN with impaired renal function. The genesis of left-sided hydrothorax with

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collapse of the lung, however, is not entirely clear. It is logical to assume that this is also a manifestation of hemostasiological disorders with thrombosis in the pulmonary artery system not only on the right, but also on the left.

As is known, antiphospholipid syndrome (APS) is an autoimmune disease of a systemic nature, in which special antibodies (APL - AT) are formed to phospholipids, which are structural components of the cell membranes of the human body, which are part of the nervous tissue, blood vessels, blood components, and participate in transport of cholesterol and fatty acids play a critical role in the blood clotting process. To date, the reasons for the development of APS have not been fully elucidated; only the main factors that play the role of triggers in the development of this pathology are known. These include autoimmune diseases (systemic lupus erythematosus, systemic scleroderma, rheumatoid arthritis, etc.), most bacterial and viral infections (in this case, the Sars - Cov -2 virus), etc. The classification of aPL syndrome includes the identification of primary and secondary aPL (associated for the above reasons). The following serological variants of APL are also distinguished: seropositive (presence of anticardiolipin antibodies and/or lupus anticoagulant) and seronegative (with the presence of antiphospholipid antibodies). The development of the pathological process in aPL is explained by the "two-hit" theory. The first blow is due to the high content of APL-ATs, which reduce the activity of proteins that ensure the stability of anticoagulant processes. The second blow is caused by an imbalance of factors responsible for the narrowing and dilatation of blood vessels. At the same time, the production of thrombomodulin, the activity of heparin and other factors are inhibited, suppressing their antithrombotic effect. In addition, APL - AT bind to platelets, which aggravates the aggregation of these cells with their subsequent destruction, resulting in thrombocytopenia. The result of the above hemostasiological, vascular-platelet and microcirculatory disorders is an increase in blood viscosity with a cascade of recurrent systemic thrombosis in the arteries, veins and capillaries, which leads to hypoxia and dysfunction of target organs with the manifestation of clinical symptoms of APS. It has been proven that one of the target organs in aPL syndrome is the kidneys, which is explained by the large extent of their vascular bed and, accordingly, the increased possibility of localizing the thrombotic process at any level. It has been established that one of the sources of thrombus formation in the kidneys may be the inferior vena cava (as in this case), the blockage of which is often asymptomatic, which makes diagnosis difficult. With a manifest version of such occlusion, as in our patient, severe pain appears in the lumbar region and lateral abdomen, protein in the urine in

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combination with hematuria with signs of renal failure. In the pathogenesis of the formation of hypertension syndrome, renal vein thrombosis, the central place is given to the activation of the RAAS, as a reaction in response to renal ischemia and a decrease in its function, which dictates the need to include angiotensin II inhibitors in the treatment of such patients. A decrease in GFR is one of the features of nephropathy associated with APS, and the slowdown in GFR may outpace the decrease in nitrogen excretory function of the kidneys. Urinary syndrome in nephropathy within the framework of aPL is characterized by isolated proteinuria of moderate severity. It is important to note that the presence of nephrotic syndrome can be combined with APS-associated nephropathy (as in this patient). The main diagnostic criteria for diagnosing aPL syndrome include: prolongation of blood clotting time, the appearance of anticardiolipin antibodies (IgM, IgG and their ratio), lupus anticoagulant, antibodies to beta-2-glycoprotein API (IgM and IgG). The results of the above tests confirm the presence of aPL in the described patient. In addition to this, coagulogram parameters are studied; in our case, the most obvious is the level of fibrinogen. The main directions of therapeutic treatment of aPL, according to the literature, consist of glucocorticosteroids (prednisolone), correction of disturbances in the homeostasis system with antiplatelet agents (acetylsalicylic acid, dipyridamole) and anticoagulants (sodium heparin, low molecular weight heparins), including modern oral anticoagulants - direct thrombin inhibitors (dabigatran etexilate) and direct Xa inhibitors (rivaroxaban , apixaban and edoxaban), and immunosuppressive therapy (rituximab , eculizumab , belimubab), high doses of intravenous immunoglobulins, plasmapheresis. A feature of the treatment of aPL with kidney damage is the prescription of angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists for nephroprotective purposes (not only antihypertensive purposes). The complex treatment of this patient with immunosuppressive goals included combined pulse therapy (glucocorticosteroid + cytostatic), massive nephroprotective therapy in combination with active anticoagulant and antiplatelet therapy. The long-term prognosis for APS is determined mainly by recurrent thrombosis, which can occur in less than 1/3 of cases, sometimes even during antithrombotic therapy.

Conclusions: In this clinical case, there was an underestimation of homeostasiological disturbances in the blood coagulation system in a patient with chronic glomerulonephritis who had Covid -19. Timely interpretation of systemic thrombosis in the post-Covid period would make it possible to diagnose secondary aPL at the initial stage of its manifestations. Late clinical diagnosis led to delayed

implementation of active anticoagulant and antiplatelet therapy in combination with combined immunosuppressive therapy in this patient.

Recommendations: In the case of a patient with a viral infection Covid-19, careful monitoring of hemostasiological parameters and the functional state of the kidneys is necessary in order to prevent thrombus formation and aPL, especially in patients with a nephrological history.

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