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A clinical case of thrombotic syndrome in a patient with chronic kidney disease in the terminal stage

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Abstract: *thrombotic syndrome is a frequent problem in patients with kidney damage, especially in the terminal stage, when the issue of vascular access for the hemodialysis procedure is extremely relevant. The clinical case presented by us with repeated thrombosis of an arteriovenous fistula demonstrates the algorithm of diagnostic search for the causes of thrombotic syndrome. The purpose of the work is to draw the attention of doctors to modern diagnostic tests for thrombotic syndrome with the help of genetic tests, to report a clinical case of vascular access thrombosis in a patient with chronic kidney disease in the terminal stage against the background of a combination of mutations in the genes of the hemostasis system and an increase in blood homocysteine.*

Key words: Chronic Kidney Disease; Thrombosis; Hyperhomocysteinemia; Hemodialysis; genetic analysis.

Introduction

A patient with chronic kidney disease (CKD) may have a hemostasis disorder in the form of both thrombosis and bleeding [1, 2, 3]. Thrombotic syndrome is an actual problem in nephrological patients, especially in the terminal stage of renal failure, when vascular access is required for hemodialysis [3]. In the management of such patients, there are many complications from the cardiovascular system, including thrombosis of the arteriovenous fistula. Frequent venipunctures, blood thickening due to the ultrafiltration process, the use of erythropoietins, endothelial dysfunction, thrombocytopathies, coagulopathy, blood pressure instability, and others stand out among the causes of thrombotic syndrome in a patient treated with hemodialysis [3, 4]. Recently, the attention of researchers has been focused on other factors of thrombotic syndrome, such as blood homocysteine, deficiency of plasma coagulation factors, imbalance of tissue plasminogen activators and

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genetic factors of thrombophilia [2, 4, 5, 6, 7, 8, 9].

Homocysteine is an amino acid formed by a cascade of biochemical transformations from methionine (Scheme 1), and serum total homocysteine levels are affected by the presence or absence of vitamins B6 and B12 and folic acid. Hyperhomocysteinemia is an independent risk factor for many diseases, including thrombosis [5, 7, 8, 9, 10].

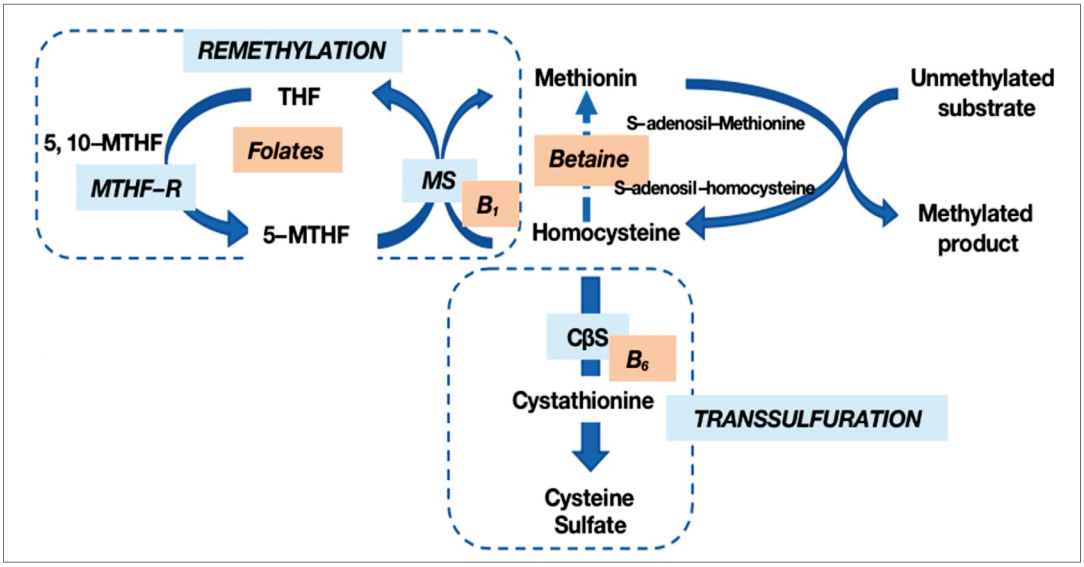
In the case of tactics and diagnostic search for thrombotic syndrome, ultrasonography of vessels, coagulogram parameters, platelet indicators, determination of D-dimer are often used in the doctor's practice. In a patient with CKD, the cause of thrombosis can be a complex of risk factors, and often they remain undefined, and only the fact of vascular thrombosis is determined. We offer consideration of a clinical case of stages of diagnostic search for thrombotic syndrome in a patient with CKD. The patient gave written informed consent for the publication of the results of his examination.

The purpose of the work is to report a clinical case of thrombosis of a vascular access in a patient with chronic kidney disease in the terminal stage against the background of a combination of mutations in the genes of the hemostasis system and an increase in blood homocysteine.

Clinical case

Patient S., 36 years old, diagnosed with stage 5 CKD, hemodialysis sessions since 2022. During the first 6 months, there were 2 episodes of arteriovenous fistula thrombosis with the need for re-forming a new vascular access. The first episode of thrombosis occurred at the pre-dialysis stage of planned preparation for renal replacement therapy methods – the patient developed an arteriovenous fistula thrombosis on the 5th day of the postoperative period (formation of an arteriovenous fistula in the lower part of the left forearm). Arteriovenous fistula revision and thrombectomy were performed. The second episode of thrombosis occurred 5 months after the initiation of dialysis therapy (hemodialisis sessions – 3 times a week for 4 hours on a standard dose of heparin). Repeated operation of foaming of the arteriovenous fistula in the middle third of the forearm was performed. In the anamnesis, at the age of 12, he suffered from hemorrhagic vasculitis after angina with damage to the skin, joints, and kidneys. According to the extract from the children's hospital of the rheumatology department, it is described as a severe form with the use of glucocorticosteroids.

Taking into account episodes of thrombosis and vasculitis in the anamnesis, a thorough comprehensive examination of the patient



Scheme 1. Homocysteine (Hcy) metabolism. Hcy is remethylated into methionine (Met) by methionine synthase (MS) in the presence of vitamin B12 and folates; transsulfuration by cystathionine-β-synthase (CβS), whose cofactor is vitamin B6, allows Hcy to be transformed into cysteine (Cy) and then into sulfate. MTHF-R: methylenetetrahydrofolate reductase.

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was carried out in order to find the cause of thrombophilia – verification of the variant of systemic vasculitis, verification of the presence of antiphospholipid syndrome and a thorough analysis of the state of the hemostasis system in the following chronology. At the first step, general clinical research methods (coalulological blood test, D-dimer, platelet count). Coagulation of blood provides us with information about the state of plasma hemostasis, the tendency to thrombosis or bleeding (Figure 1), but does not indicate the cause of thrombosis.

At the second step, taking into account the anamnesis, verification of systemic vasculitis and antiphospholipid syndrome was carried out (determination of antineutrophil antibodies – Ig G to myeloperoxidase and Ig G to proteinase-3, diagnostic panels of indicators of antiphospholipid

Coagulogram

31.08.2022 11:56

Investigation	Result	Unit	Reference value
Prothrombin Time (PT)	15.9	sec	9-14.6
Quick-type PT (%)	70.7	sec	70-130
Activated Partial Thromboplastine Time (APTT)	24	sec	23.2-35.2
Thrombin Time (TT)	19.1	sec.	15.6-22.2
Fibrinogen (FIB)	2.51	g/l	2-4
International Normalized Ratio (INR)	1.26	U	0.8-1.2
D-Dimer	0.282	mkg/ml	0-0.5

Figure 1. Coagulogram of the patient.

Акредитація згідно
ДСТУ EN ISO 15189:2015 (EN ISO 15189:2012, IDT)

Результати досліджень

Дата замовлення: **27.03.2023 07:19** Оформлено: **у відділені**

Клієнт:

Дата народження: **1987** Вік: **35 Y** Стать: **Чоловіча**

Показник	Результат	Од.	Референтний інтервал
Пакет №5.10 (Системні васкуліти - ANCA)			Індикатор зони підвищеної уваги
Мієлопероксидаза (MPO), антитіла IgG	**< 2**	Од/мл	<20.0 - негативний результат ≥20.0 - позитивний результат Метод: Імуноферментний аналіз (ІФА, ELISA) Реагенти: Euroimmun (Німеччина) Аналізатор: EUROIMMUN Analyzer I (Німеччина)
Протеїназа 3 (PR3), антитіла IgG	**< 2**	Од/мл	<20.0 - негативний результат ≥20.0 - позитивний результат Метод: Імуноферментний аналіз (ІФА, ELISA) Реагенти: Euroimmun (Німеччина) Аналізатор: EUROIMMUN Analyzer I (Німеччина)
Базальна мембрана гломерулярного апарату (GBM), антитіла IgG	**< 2**	Од/мл	<20.0 - негативний результат ≥20.0 - позитивний результат Метод: Імуноферментний аналіз (ІФА, ELISA) Реагенти: Euroimmun (Німеччина) Аналізатор: EUROIMMUN Analyzer I (Німеччина)

Indicator	Result	Unit	Reference value
Myeloperoxidase (MPO), antibodies IgG	<2	U/ml	<20.0 – negative >=20.0 – positive
Proteinase 3 (PR3), antibodies IgG	<2	U/ml	
Glomerular basement membrane (GBM), antibodies IgG	<2	U/ml	

Figure 2. Verification of systemic vasculitis.

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syndrome – lupus anticoagulant, IgM and IgG antibodies to cardiolipin, IgG antibodies to β2-glycoprotein). Since the patient was diagnosed with hemorrhagic vasculitis in childhood, a study of proteinase 3 and myeloperoxidase titers in the blood was conducted, as classic laboratory criteria for the classification of systemic ANCA-associated vasculitis [11], which did not reveal any deviations from the norm (Fig. 2).

The next step of the diagnostic search was to assess the probability of antiphospholipid syndrome as the cause of recurrent thrombosis. An increase in the level of lupus anticoagulant in the blood (Fig. 3) is considered, according to the classification criteria of antiphospholipid syndrome (2023), as one of the entry criteria for this disease [12], however, the patient did not have enough other criteria to confirm the specified pathology.

At the next stage of the diagnostic search, the patient was assigned to determine the blood homocysteine level and genetic analysis of

РЕЗУЛЬТАТИ ДОСЛІДЖЕНЬ

Пацієнт:		**Лаб. № замовлення**	
Дата народж.	1987	**Код замовлення:**	-
Стать:	Чоловіча	**Дата замовлення:**	01.06.2023 7:39
Коментарі:			

Назва дослідження	Результат	Одиниці вимірювання	Референтні значення	Коментарі
Комплекс №28 "Діагностика антифосфоліпідного синдрому"				
Вовчуковий антикоагулант Первинна проба: венозна кров	**1.232***		< 1.2	
Вовчуковий антикоагулант підтверджуючий тест	1.121			
Нормалізоване ВА співвідношення	1.099 Вовчуковий антикоагулант негативний		< 1.2	<1,2 негативний 1,2 - 1,5 слабо позитивний 1,5 - 2,0 помірно позитивний >2,0 високо позитивний
Антитіла до кардіоліпіну IgM Первинна проба: венозна кров Метод ELIA	1.3 негативний	MPL-U/ml	< 10	<10 негативний 10-40 сумнівний >40 позитивний
Антитіла до кардіоліпіну IgG Первинна проба: венозна кров Метод ELIA	2.7 негативний	GPL-U/ml	< 10	<10 негативний 10-40 сумнівний >40 позитивний
Антитіла до В2-глікопротеїну IgG Первинна проба: венозна кров Метод ELIA	4.0 негативний	U/ml	< 7	<7 негативний 7-10 сумнівний >10 позитивний

Indicator	Result	Unit	Reference value	Comment
Lupus anticoagulant (primary sample – venous blood)	1.232		<1.2	<1.2 – negative 1.2-1.5 – weakly positive 1.5-2.0 – moderately positive >2.0 – highly positive
Lupus anticoagulant (confirmatory test)	1.121		<1.2	
Normalized LA ratio	1.099		<1.2	
Antibodies to cardiolipin IgM (primary sample – venous blood)	1.3	MPL-U/ml	<10	<10 – negative 10-40 – uncertain >40 – positive
Antibodies to cardiolipin IgG (primary sample – venous blood)	2.7	GPL-U/ml	<10	<10 – negative 10-40 – uncertain >40 – positive
Antibodies to β2-glycoprotein IgG (primary sample – venous blood)	4.0	U/ml	<7	<7 – negative 7-10 – uncertain >10 – positive

Figure 3. diagnostic of antiphospholipid syndrome.

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Indicator	Mutation (absent/ discovered)	Comment
Gen F2-prothrombin (20210 G>A) factor II of blood clotting	absent	Absence of mutation – normal Heterozygous carrier – risk factor Homozygous carrier – risk factor
Gen F5(1691 G>A) factor V of blood clotting	absent	
Gen F7(10976 G>A) factor VII of blood clotting	absent	
Gen F13 A1 (103 G>T) factor XIII of blood clotting	discovered (heterozygous carrier)	
Gen FGB-Fibrinogen (455 G>A) фактор I blood clotting	discovered (heterozygous carrier)	
Gen GP1 BA (482 C>T) platelet glycoprotein 1b	absent	
Gen Serpin1 PAI-1 (675 5G>4G) tissue plasminogen activator antagonist	discovered (homozygous carrier)	
Ген ITGB3-b-інтегрин(1565 C>T) platelet fibrinogen receptor	absent	

Figure 4. Diagnostic genetic analysis of mutations in the genes of the hemostasis system.

mutations in the genes of the hemostasis system. An increase in the level of homocysteine – 34,4 mcmol/l found in the patient can be considered as a significant factor that increases the risk of thrombosis. Genetic analysis of mutations in genes of plasma coagulation factors (Fig. 4) revealed gene polymorphisms: F13A1 (103G>A) (factor XIII of blood coagulation – heterozygous carrier), FGB-fibrinogen (455G>A) (factor I of blood coagulation – heterozygous carrier), Serpin1(PAI-1) (675 5G>4G) (antagonist of tissue activator plasminogen – homozygous carrier).

In the correction of hyperhomocysteinemia folate therapy which was prescribed to the patient, is of leading importance [13]. At the same time during this therapy repeated thrombosis was not observed.

Discussion and Conclusions

This clinical case is of great practical importance due to the fact that in the majority of cases of thrombophilia, the causes of the disease remain undiagnosed and worsen the patient's prognosis. Given the high frequency of coagulopathy in a patient with CKD, a diagnostic algorithm for finding the level of damage to the hemostasis system in thrombophilia is necessary: platelet parameters, coagulogram, D-dimer, systemic vasculitis panel, antiphospholipid syndrome panel, homocysteine, genetic analysis of hemostasis system gene mutations. In addition to routine methods of research, today methods of genetic research of gene mutations responsible for a certain defect in various links of the hemostasis system have become available. Examinations do not allow to definitively determine the role of certain factors of thrombophilia in the occurrence of thrombosis in this patient, however, the available possibilities of therapeutic interventions in such patients still allow, in some cases, targeted correction of hemocoagulation disorders. In the described case long-term follow-up is required regarding the effectiveness of folates in the prevention of thrombosis.

Conflicts of interest

Authors have no conflict of interest to daclare.

Consent to publication

All authors have read and approved the final version of the manuscript. All authors have agreed to publish this manuscript.

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of article.

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Тромботичний синдром у пацієнта на хронічну хворобу нирок в термінальній стадії: клінічний випадок

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Анотація. *Тромботичний синдром є частою проблемою у пацієнтів з ураженням нирок особливо в термінальній стадії коли питання судинного доступу для проведення процедури гемодіалізу є надзвичайно актуальним. Представлений нами клінічний випадок з повторним тромбозом артеріовенозної фістули демонструє алгоритм діагностичного пошуку причин тромботичного синдрому. Мета роботи – привернути увагу медиків до сучасних діагностичних тестів тромботичного синдрому за допомогою генетичних тестів, повідомити про клінічний випадок тромбозу судинного доступу у хворого на хронічну хворобу нирок в термінальній стадіїна тлі поєднання генних мутацій системи гемостазу та підвищення гомоцистеїну крові.*

Ключові слова: хронічна хвороба нирок, тромбоз, гіпергомоцистеїнемія, генетичний аналіз.