DISSEMINATED HIV-ASSOCIATED VENOUS THROMBOSIS (A CASE REPORT)

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Introduction. In 1983, Robert Gallo (USA) and Luc Montagnier (France) discovered the human immunodeficiency virus (HIV). Today, about 39 million people are living with HIV worldwide. Thanks to antiretroviral therapy (ART), HIV has become a manageable chronic condition for most patients. However, the number of associated complications, including cardiovascular disease and thrombosis, is increasing. HIV-associated venous thrombosis, such as deep vein thrombosis and pulmonary embolism, requires attention and research due to their serious consequences.

The purpose was to summarize, analyze, and demonstrate the clinical sequence, diagnostic difficulties and treatment of a rare case of disseminated venous thrombosis in the setting of HIV infection.

Materials and methods. Periodical medical publications, patient records, and materials of scientific and practical conferences were used. Research methods: historical, bibliographic, systematic approach, analytical, generalization.

Results. The article analyses in detail the data on a severe complication of HIV infection - disseminated venous thrombosis. To establish the final diagnosis, differential diagnosis with infectious, rheumatological, and myeloproliferative diseases was performed. As a result of the differential diagnosis, a multidisciplinary team of doctors established homozygous carriage of the MTHFR 1298 gene, which determines an increased risk of thrombosis. The addition of HIV infection could be a trigger for the development of severe thrombosis with impaired internal organ function.

Conclusions. All countries of the world continue to face the problem of HIV infection, which requires constant detection among the population, including military personnel. In the case of thrombosis under consideration, both HIV infection itself (reduced CD4 T-cell counts, late HIV detection) and genetic factors could be the cause. The patient's multidisciplinary management proved to be effective, which allowed him to achieve a positive result, and his fight against the disease will continue.

Key words: human immunodeficiency virus, thrombosis, MTHFR 1298, differential diagnosis.
the anterior abdominal wall, severe general weakness, dry mouth, fever up to 39.1°C.

From the anamnesis it is known that the deterioration of the condition in the form of swelling of both lower extremities, weakness in the legs, and pain in both legs was noted in August 2023. In September 2023, he noticed a heaviness in his abdomen, on 23.09.2023 he developed a syncopal state, for which he was treated in the Military Medical Clinical Centre of the Northern Region. On 03.10.2023, according to ultrasound and multispiral computer tomography, he was diagnosed with acute thrombosis of the infrarenal division of the inferior vena cava and portal vein. Initially, the patient received anticoagulant therapy: heparin 5000 IU every 4 hours for the first 5 days with a transfer to rivaroxaban 30 mg per day. Indicates a complicated heredity - the presence of lower limb vascular disease in the father, which led to the amputation of one of the limbs. During the mobilisation call-up, HIV testing was not performed (according to the patient).

Transferred on 18.10.23 to the NMMCC "GVKG". Objectively on admission: the general condition of moderate severity. Body temperature 38.8 °C. Heart rate 118 per min. Blood pressure 130/80 mmHg, SpO2 98% / St. localis: skin of both thighs, legs, anterior abdominal wall - cyanotic. In the area of the anterior abdominal wall - increased vascular pattern. There is marked edema of both feet, legs, thighs. Satisfactory pulsation is determined on the arteries of the lower and upper extremities. The symptoms of Homans and Moses are positive on both sides. Elastic bandaging of both lower extremities.

On the day of admission, according to the ultrasound of the abdomen, there were signs of thrombosis of the v. portae with recanalisation of blood flow, v. cava inferior to the level 6-7 cm above the navel. Hepatomegaly, steatohepatosis, chronic pancreatitis.

Duplex scan of the veins of the lower extremities dated 18.10.2023: at the time of the examination, ultrasound signs of phlebothrombosis of the deep veins of both lower extremities from the level of the middle third of the lower legs to the level of the confluence of the common iliac veins without signs of recanalisation of blood flow.

MSCT of the chest cavity, abdominal cavity, and pelvic organs dated 18.10.2023. Pulmonary fields, diaphragmatic domes, mediastinal organs, heart, aorta, esophagus, tracheobronchial tree, liver, intra- and extrhepatic ducts, common bile duct without features. Portal vein - 1.9 cm, right branch with signs of thrombosis, contrasted fragmentarily in the proximal parts, proximal parts of the left branch at the level of compliance with the presence of thrombi. The portal vein is clearly visible at the level up to the level of conflict with the splenic artery. The superior mesenteric vein is clearly contrasted only in the proximal parts, otherwise it is thrombosed and unevenly dilated. The gallbladder, spleen, pancreas, stomach, small and large intestine are also unremarkable. The splenic artery and vein are not dilated, the vein at the level of confluence contains filling defects. Adrenal glands, kidneys, renal vein, renal arteries, bladder, prostate gland are of typical location, without any features. An irregularly shaped saccular aneurysm with clear contours measuring 3.2 × 2.77 × 2.76 cm was detected along the anterior-upper edge of the right renal vein, without any features. The descending aorta and all its branches are evenly contrasted. The inferior vena cava is clearly visible from the level of the renal veins, distally its lumen is sharply narrowed and fragmented. The common iliac, external and internal iliac veins appear unevenly dilated, are not contrasted, and contain small parietal calcifications. In the lumen of the inferior vena cava at the level of the suprarenal segment, a parietal calcification with a conditional diameter of up to 0.7 cm and a length of up to 1.7 cm is determined.

At the time of the examination, MSCT showed signs of thrombosis of the right branch of the portal vein, superior mesenteric vein, proximal splenic vein, inferior vena cava below the confluence of the renal veins, saccular aneurysm of the right renal vein.

Echocardiography dated 19.10.2023: the heart cavity and valves were unchanged. The left ventricular myocardial contractility was satisfactory (left ventricle ejection fraction - 55%), and no areas of dyskinesia were detected.

Taking into account the examination on the day of admission, the diagnosis of acute thrombosis of the portal vein, superior mesenteric vein, right renal vein, infrarenal division of the inferior vena cava, iliofemoral, femoral-popliteal and tibial segments on both sides was clarified.

The haemogram showed normochromic normocytic anemia (80 g/l), slight leukocytosis (10.2 × 10⁹/L), with a shift to neutrophils in the formula, thrombocytosis (480 - 500 × 10⁹/L). The coagulogram showed a periodic decrease in prothrombin index levels, an increase in international normalised ratio, and activated partial thromboplastin time levels. The biochemical blood test showed elevated levels of C-reactive protein (up to 100 mg/L), ferritin (up to
1400 μg/L), GGT (up to 850 U/L) and liver transaminases (ALT - 104 U/L, AST - 111 U/L), which normalized in the course of symptomatic (hepatoprotective, antibacterial) therapy.

The patient continued to receive rivaroxaban (30 mg per day), symptomatic therapy and a course of broad-spectrum antibiotics (25.10.-01.11.2023). After the acute period of thrombosis, a diagnostic search was carried out to identify the cause of such total thrombosis and to make a differential diagnosis between diseases that could provoke thrombosis (diseases of the blood system, connective tissue, infectious diseases, oncological pathology).

During the entire observation period, febrile fever of up to 38-39.8°C was present. Therefore, our efforts were primarily aimed at finding infectious diseases. The procalcitonin test revealed an elevated level of 3.4 ng/mL (25.10.23). RW from 19.10.2023: negative. No viral hepatitis infection was detected. Urine culture of 30.10.2023: bacteriuria was not detected. Blood culture dated 01.11.2023: no growth of microorganisms was detected. Pharyngeal culture of 30.10.2023: Candida albicans 104 CFU/mL. Antibodies to cardiolipin Ig G from 27.10.2023: 3.8 GLP-U/mL (negative at < 10), antibodies to B2-glycoprotein Ig G from 27.10.2023: 1.1 U/mL (negative at < 7), antibodies to B2-glycoprotein Ig M from 27.10.2023: < 2.9 U/mL (negative at < 7). Lupus anticoagulant from 27.10.2023 - 1.906 (normal up to 1.2). The patient was consulted by a rheumatologist - no data were found in favour of antiphospholipid syndrome.

The next step in the differential diagnosis was to determine hereditary thrombophilia

<table>
<thead>
<tr>
<th>Polymorphism of thrombophilia genes</th>
<th>Result</th>
<th>Reference values</th>
</tr>
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<tbody>
<tr>
<td>Factor 2 Prothrombin 20210 G&gt;A</td>
<td>G/G</td>
<td>G/G – normal genotype</td>
</tr>
<tr>
<td>Factor 5 Leiden 1691 G&gt;A</td>
<td>G/G</td>
<td>G/G – normal genotype</td>
</tr>
<tr>
<td>Factor 5 R2 4070 A&gt;G</td>
<td>A/A</td>
<td>A/A – normal genotype</td>
</tr>
<tr>
<td>Factor 5 5279 A&gt;G</td>
<td>A/A</td>
<td>A/A – normal genotype</td>
</tr>
<tr>
<td>MTHFR 677 C&gt;T</td>
<td>C/C</td>
<td>C/C – normal genotype</td>
</tr>
<tr>
<td>MTHFR 1298 A&gt;T</td>
<td>C/C</td>
<td>C/C – homozygote</td>
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A study of thrombophilia gene polymorphism revealed homozygous carriage of the MTHFR 1298 gene, responsible for the activity of the methylene tetrahydrofolate reductase enzyme. The genetic defect of this gene leads to a decrease in the functional activity of the MTHFR enzyme, which is accompanied by a violation of the folate cycle. Folate cycle disorders lead to the accumulation of homocysteine in cells and blood plasma. Homocysteine causes an increased risk of thrombosis.

To exclude myeloproliferative diseases (MPDs), which often have thrombotic complications, histological and molecular genetic studies were performed. According to the histological examination of the trepanobiopsy of the hypochondrium dated 07.11.23, no clear signs of myeloproliferative disease were found. No mutations of V617F of the JAK2 gene and types 1, 2 of the SALR gene were detected in peripheral blood cells.

During the examination for antibodies to HIV type 1/2 on 19.10.23, a result was obtained that required clarification, which took place on 30.10.23 (positive). He was consulted by an infectious disease specialist, and the number of CD lymphocytes was determined on 31.10.23: absolute CD3+/CD4+ (T-helper) 114.0 kl/mL (normal 400-1800 kl/mL); relative CD3+/CD4+ (T-helper) 13.0%, which was indicative of severe immunodeficiency.

On 02.11.23, the patient was transferred to the Infectious Diseases Clinic, where he continued treatment. At this time, febrile fever was observed with daily fluctuations of up to 38.0°C, and in the period from 12 to 15 November it reached 39.9°C, which did not affect the patient’s general condition. Symptomatically, he was treated with ibuprofen 400mg per day without any significant effect. He received two short courses of fluconazole due to manifestations of oropharyngeal candidiasis.

He was consulted at the L.V. Gromashevsky Institute of Epidemiology and Infectious Diseases of the National Academy of Medical Sciences of Ukraine and diagnosed: Chronic retroviral infection, clinical stage III, recurrent oral candidiasis. For the first time in his life, he was prescribed lifelong antiretroviral therapy (ART), which was started on 14.11.23 in the dolutegravir/lamivudine/tenofovir
(DTG/3TC/TDF) regimen 50/300/300 mg, 1 tablet once daily.

Additionally, the patient underwent a blood test (TORCH) dated 02.11.23: EBV VCA-IgG detected 12.2, EBV VCA-IgM not detected, HSV 1/2 IgG detected 5.5, HSV 1/2 IgM not detected, CMV IgG detected 3.4, CMV IgM not detected, TOXO IgG detected 115.0, TOXO IgM not detected. Blood test by PCR to herpes group from 31.08.23: no herpesvirus genetic material was detected.

In terms of treatment, ART was preceded by prophylactic use of trimethoprim/sulfamethoxazole at a dose of 960 mg per day, taking into account low levels of CD4+ T-lymphocytes. Taking into account the impossibility of excluding atypical mycobacteriosis from 7.11.23 to 12.11.23, the patient received azithromycin (without significant effect on fever). Along with DTG/3TC/TDF (ART), from 14.11.23 he received isoniazid 300 mg per day as isoniazid preventive therapy (IPT) in combination with a daily dose of B vitamins. All the time, he was treated with elastic bandaging of the lower extremities with the transition to wearing compression stockings, accompanied by rivaroxaban (20 mg per day) and venotonic (diosmin/hesperidin, 1000 mg per day). Increased hepatic transaminases were considered to be a consequence of portal vein thrombosis and were corrected by taking ursodeoxycholic acid at a daily dose of 750 mg.

In the setting of concomitant ART+IPT, body temperature normalised and periodically rose to subfebrile levels (Figure 1).

![Figure 1. Combined graph (temperature - treatment measures)](image)

According to the order of the head of the NMMC "GVKG", the patient was examined by a therapeutic specialized medical evaluation board and found unfit for military service with exclusion from military registration on the basis of Articles 5a, 42a of Order of the Minister of Defence of Ukraine No. 402 of 2008 (as amended).

Diagnosis at discharge: [B20.9] Chronic retroviral infection, clinical stage II, phase of immune decompensation (CD4+ T-lymphocytes 114 cells/mL). Oropharyngeal candidiasis. Chronic herpesvirus infection associated with HSV 1/2 (IgG+, IgM-, DNA-), EBV (IgG+, IgM-, DNA-), CMV (IgG+, IgM-, DNA-), latent course, integration phase.

Primary chronic toxoplasmosis (IgG+, IgM-), latent course. Anaemia of chronic disease, moderate severity. [I82.8] Thrombosis of the inferior vena cava (below the confluence of the renal veins), portal vein, superior mesenteric vein, proximal splenic vein and right renal vein. Iliofemoral and popliteal segments on both sides, varicose and edematous form, occlusion stage with significant impairment of blood circulation and function. High genetic risk of thrombophilia (C/C - homozygote for MTHFR 1298 mutation). Reactive (drug-induced) hepatitis, cholestatic variant, with moderate liver dysfunction. Non-alcoholic fatty liver disease. Condition after acute kidney injury (AKIN) grade 3 dated 03.10.23. Angiopathy of the retina of both eyes.

To implement the decision of the medical evaluation board, after approval of the certificate of illness, the patient was discharged to the military unit on 30.11.23 with appropriate recommendations for the two main diagnoses.

Discussion. This observation confirms the well-known fact that the presence of a chronic infectious disease, namely HIV, increases the risk of venous thrombosis (VT). For example, among PLHIV, the risk of developing VTE is 2-10 times higher [16], and people with low CD4+ cells are more likely to suffer from it [19, 20]. Other risk
factors for VT in PLHIV are malignancies and co-infections [17, 21]. According to Virchow's triad, there are three main factors for the development of VT: hypercoagulability, endothelial dysfunction, and blood stasis [22]. In PLHIV, the most important factors in the development of VT are hypercoagulability and endothelial dysfunction [4]. It has been shown that leukocytes, namely monocytes and neutrophils, are involved in the process of thrombus formation [23-25]. This process is called immunothrombosis [25]. As a consequence, activated monocytes express tissue factor (TF), which is a trigger of DVT in pathological conditions [26-28].

Endothelial cells normally secrete various anticoagulant proteins, such as TF inhibitor, thrombomodulin, endothelial protein C receptor, and antithrombin [29]. The effect of inflammatory mediators on endothelial cells converts the endothelium from an anticoagulant surface to a procoagulant one by decreasing thrombomodulin expression and increasing TF release [30,31]. PLWH are usually deficient in anticoagulant proteins such as protein S, protein C, heparin cofactor II and antithrombin. The most likely cause of this is opportunistic infections and malignancies [18]. This hypothesis is supported by a clear link between VT and low CD4+ T-cell counts in PLHIV [16]. PLHIV also have autoantibodies to protein S, antiphospholipid antibodies, and lupus anticoagulant [18]. These autoantibodies are also implicated in the impaired anticoagulant function of protein S, protein C and antithrombin [32].

The number of monocytes in PLHIV increases [33]. Studies show that monocytes of PLWH express TF [33-36]. Expression of TF by monocytes correlates with plasma IL-6, T-cell activation, and viremia in PLHIV [33]. In addition, monocyte TF expression was correlated with plasma levels of D-dimer and sCD14, as well as with HIV RNA levels [36]. It has been shown that the level of TF-expressing monocytes in PLWH is elevated and significantly higher than in monocytes of healthy individuals [37]. It is a significant fact that ART does not affect the level of TF-expressing monocytes [4], and the rate of thrombotic complications remains constant in PLHIV both on and off ART.

Thus, monocytes are a key actor in the activation of TF. In addition, TF-activated extracellular vesicles (EVs) [38] released from activated monocytes can bind to platelets, effectively transferring TF to platelets [39]. Platelets of PLHIV are more likely to contain TF than platelets of healthy people, and the level of TF-positive platelets correlates with TF expression in monocytes [40].

In summary, immune system dysfunction and chronic inflammation caused by HIV lead to monocyte activation and expression of proinflammatory cytokines such as IL-6. Chronic inflammation leads to endothelial cell dysfunction and platelet activation. Activated monocytes express the procoagulant protein TF. Monocyte TF and monocyte-derived TF-positive EVs can activate the coagulation system. The activated coagulation system and activated platelets contribute to venous thrombosis.

Conclusions: HIV infection remains relevant for Ukraine and requires timely detection in the general population, especially among the contingent to be mobilized. In the clinical case reviewed, the most likely causes of thrombosis were both HIV infection (low CD4 T-cell counts, late presenters - late detection of HIV) and constitutional and genetic prerequisites. The patient's management as part of a multidisciplinary team proved to be effective, the patient received adequate treatment, which had a positive effect, and his fight for life will continue.

References
Розповсюджений ВІЛ-асоційований венозний тромбоз (клінічний випадок)

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Вступ. У 1983 році Роберт Галло (ШСА) та Люк Монтаньє (Франція) відкрили вірус імунодефіцит людини (ВІЛ). На сьогоднішній день близько 39 млн людей живуть у світі з вірусним імунодефіцитом людини. Завдяки антиретровірусній терапії (АРТ), ВІЛ перетворився на керований хронічний стан для більшості хворих. Однак, зростає кількість супутніх ускладнень, зокрема серцево-судинних захворювань та тромбозів. ВІЛ-асоційовані венозні тромбози, такі як тромбоз глибоких вен та тромбоемболія легеневої артерії, потребують уваги через її серйозні наслідки.

Мета роботи: необхідність узагальнити, проаналізувати та продемонструвати особливості клінічного перебігу, труднощі діагностики, а також особливості лікування рідкісного випадку розповсюджених венозних тромбозів на фоні ВІЛ-інфекції.


матеріали та методи. Використані періодичні медичні видання, історії хвороби пацієнтів, матеріали науково-практичних конференцій. Методи дослідження: історичний, бібліографічний, системного підходу, аналітичний, узагальнення.

Результати. У статті детально проаналізовано дані про важке ускладнення при ВІЛ-інфекції – розповсюджений венозний тромбоз. Для встановлення заключного діагнозу було проведено диференційну діагностику з інфекційними, ревматологічними, мієлопроліферативними захворюваннями. В результаті проведення диференційної діагностики мультидисциплінарною командою лікарів було встановлено гомозиготне носійство гену MTHFR 1298, який визначає підвищений ризик виникнення тромбозів. Приєднання ВІЛ-інфекції могло бути тригером розвитку тяжкого тромбозу з порушенням функції внутрішніх органів.

Висновки. Всі країни світу продовжують стикатися з проблемою ВІЛ-інфекції, яка потребує постійного виявлення серед населення, в тому числі військовослужбовців. У випадку тромбозу, що був розглянутий, причиною могли бути як сама ВІЛ-інфекція (знижені рівні CD4 T-лімфоцитів, пізнє виявлення ВІЛ), так і генетичні фактори. Мультидисциплінарне ведення пацієнта виявилося ефективним, що дозволило досягти позитивного результату, і його боротьба з захворюванням триватиме.

Ключові слова: вірус імунодефіциту людини, тромбоз, MTHFR 1298, диференційна діагностика.

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