Wiadomości Lekarskie
Medical Advances

VOLUME LXXVI, ISSUE 9, SEPTEMBER 2023
Official journal of Polish Medical Association has been published since 1928

ISSN 0043-5147
E-ISSN 2719-342X

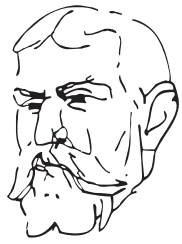
INDEXED IN PUBMED/MEDLINE, SCOPUS, EMBASE, EBSCO, INDEX COPERNICUS,
POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

Wiadomości Lekarskie
Medical Advances

VOLUME LXXVI, ISSUES 9, SEPTEMBER 2023
Official journal of Polish Medical Association has been published since 1928

ISSN 0043-5147
E-ISSN 2719-342X

ALUNA Publishing



Memory of
dr Władysław
Biegański

Wiadomości Lekarskie is abstracted and indexed in: PUBMED/MEDLINE, SCOPUS, EMBASE, INDEX COPERNICUS, POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

The journal Wiadomości Lekarskie is cofinanced under Contract No.RCN/SN/0714/2021/1 by the funds of the Minister of Education and Science

Wiadomości Lekarskie
Medical Advances

Distribution and Subscriptions:
Bartosz Guterman prenumerata@wydawnictwo-aluna.pl
Graphic design / production:
Grzegorz Sztank fajne.work

Publisher:
ALUNA Publishing
ul. Przesmyckiego 29,
05-510 Konstancin – Jeziorna
www.wydawnictwo-aluna.pl
www.wiadomoscilekarskie.pl
www.wiadlek.pl

CONTENTS

REVIEW ARTICLES

CASE STUDY

THROMBOTIC MICROANGIOPATHY: DIAGNOSTIC CHALLENGES IN THE PRIMARY MULTIPLE NEOPLASM INVOLVEMENT WITH PREVALENT METASTASIS WITH GRANULOMATOSIS INFLAMMATORY FOCUSES

DOI: 10.36740/WLek202309131

Halyna V. Osyodlo[1], Svitlana A. Husieva[1], Mykhailo P. Boychak[1], Olena Antonyuk[2,3]
[1]UKRAINIAN MILITARY MEDICAL ACADEMY, KYIV, UKRAINE
[2]NATIONAL MILITARY MEDICAL CLINICAL CENTRE "MAIN MILITARY CLINICAL HOSPITAL", KYIV, UKRAINE
[3]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Patient, who died during the hospital stay, had hemoblastosis and syphilis in the reported medical history. While the patient was examined doctors suspected the presence of malignancy with unknown primary localization with multiple metastatic injuries with clinical and laboratory TTP signs (hemorrhagic syndrome, thrombocytopenia, shystocytosis, and non-immune hemolytic anemia). Despite treatment, the general patient's condition progressively worsens with increasing multiple organ decompensation signs. In the final stage of the disease course, after heart arrest and the appearance of clinical death signs CPR measures were performed according to complete guidance, but CRP had no positive effect. Biological death was constated.

Considering the criteria of the diagnostic clinical and laboratory dyad (thrombocytopenia and microangiopathic hemolytic anemia), the data of the pathological examination (multiple metastatic lesions, inflammatory process, tumor intoxication, thrombosis), the combination of manifestations of chronic myeloid leukemia, prostate cancer with multiple metastases, tertiary syphilis served as a condition for the initiation of TTP, which was of decisive importance in the development of the patient's death.

KEY WORDS: thrombotic thrombocytopenic purpura, thrombotic microangiopathy, plasma exchange therapy, ADAMTS13, von Willebrand factor

Wiad Lek. 2023;76(9):2121-2126

INTRODUCTION

Thrombotic thrombocytopenic purpura (Moschcowitz syndrome, TTP) is a minor vessels injury (microangiopathy) that is characterized by hemolytic anemia, intravascular coagulation, thrombocytopenia, injury of kidneys and nervous system [1 - 3]. According to the Chiasakul, T. & Cuker A. [4] is a rare, life-threatening disease with an incidence of approximately 2 persons per million per year. TTP has an extremely aggressive course and requires starting therapy as soon as possible (during first hours after onset). In the absence of adequate and urgent management, the lethality is high and lies at 72-94% [5]. That is why in the absence of other possible reasons for thrombocytopenia and non-immune hemolytic anemia TTP should be thought as a proved diagnosis and treatment should be started. Early adequate therapy allows to avoid life-threatening key-organ injury [6, 7].

CASE REPORT

Patient G., a 54-year-old man born in 1965, was admitted on the 15th of October 2019 to the hematological clinic of the National Military Medical Clinical Centre "Main Military Clinical Hospital" with complaints of non-severe fatigue, intermitted petechial skin rash and excessive bleeding after small injuries. He reported that 30 years ago, he had been admitted to the dermatological department for syphilitic treatment. After receiving primary therapy and leaving the dermatological department, he never checked again for the effectiveness of syphilitic treatment and was not examined by a dermatologist.

While admitted in October 2019, a general patient's condition was not bad. In the blood count test (BCT), severe anemia (RBC – 1,12×1012/l, MCV – 103 fl., hemoglobin (Hb) – 78,0 g/p), reticulocytotic changes in the blood – 45%) and thrombocytopenia (25,0×109/l) were

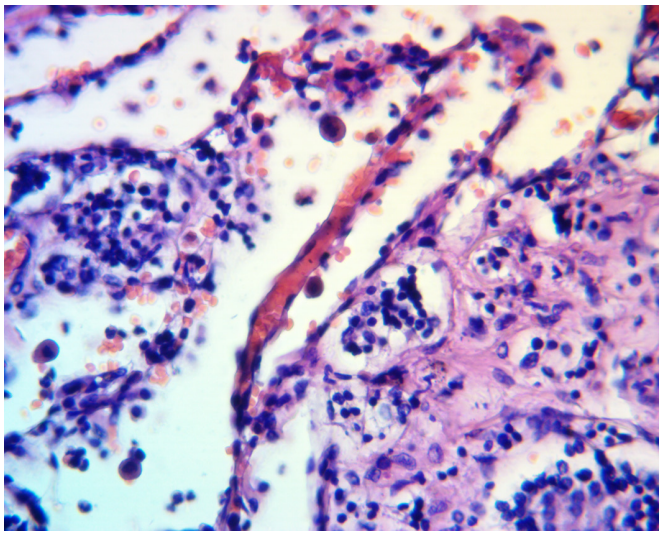


Fig. 1. Red clots in pulmonary vessel in the stage of erythrocytes agglutination (with hematoxylin and eosin, enlargement ×400).

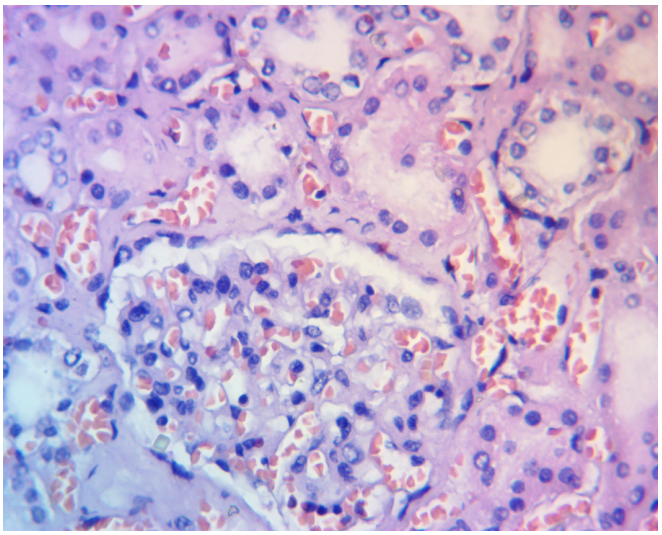


Fig. 2. Red clots in small vessels of kidney glomeruli in the stage of erythrocytes agglutination (with hematoxylin and eosin, enlargement ×400).

detected. While checking RBC morphology, shystocytosis was detected. Direct and indirect Coombs tests were negative. Myelogram reported that red bone marrow (RBM) had a few numbers of cells; megakaryocytes were absent; thrombocytes were in a small amount in the microscopic unit of view. Leuco-/erythrocytes ratio was increased up to 4.88:1 (normal range 3:1–4:1). Myeloproliferative process was suspected after performing of cytomorphological, cytochemical immunophenotype blood and RBM examining.

Chest X-ray did not report any infiltrative or volume findings in the lung parenchyma. US-findings: liver and spleen were enlarged, as well pleural effusion on the right part of the chest was observed. Finally, we received positive test results on the presence of antibodies against Treponema pallidum.

In the period of 15-23 of October 2019, the patient's general condition was quite good, but on October 24 state rapidly became worse: respiratory deficiency appeared and still progressed (dyspnoea at rest which increased with minimal physical activity). Myelogram results (October 24) reported the presence of myeloproliferative disease and recommended performing a trepan biopsy, but the last examination procedure was unavailable due to severe thrombocytopenia.

Multidetector computed tomography of the brain, chest, abdomen and pelvis helped to visualize such changes: signs of multiple segmentary bilateral pneumonia; bilateral hydrothorax (35 mm in the right and 23 mm in the left pleural spaces); hydropericardium (up to 33 mm); mediastinal lymphadenopathy (maximal sizes up to 16-19 mm); hepatosplenomegaly; rectoabdominal lymphadenopathy (maximal sizes up to 25-28 mm); ascites; generalized multiple skeletal bone involvement.

The patient was transported to the intensive care unit (ICU) as his condition rapidly worsened with pneumonia, respiratory insufficiency, bycytopenia, and severe intoxication. In the ICU patient's condition constantly was getting worse with the progression of multiple organ insufficiency. The dermatologist examined the patient, and his diagnosis was: Lues latens (latent syphilis).

On the evening of October 24th (from 5 p.m. to 11 p.m.), moderate ecchymosis appeared on the skin of the abdomen, legs and arms. Respiratory insufficiency had progressed, the patient became hemodynamically unstable, and anuria appeared, as a result, a heart arrest happened at 23:27. Cardio-pulmonary resuscitation CPR was ineffective. Biological death was constated at 23:57 on October 24th, 2019.

The pathological expertise of the body detected some macroscopic changes that could be divided into several groups:

- hemorrhage syndrome: petechial and ecchymosed hemorrhages in the skin, on the parietal pleura, on the visceral layer's pericardium, and in the epicardial adipose tissue.
- granulomatous inflammation: typical hilly layering on the diaphragmatic surface and aortic intima.
- possible (or probable) primary malignancy: subcapsular prostatic overgrowth of yellow tissue bilaterally with over 50% of prostatic involvement.
- possible (or probable) metastatic grey-yellowish injury of subpleural layers of the lung parenchyma, lymphatic nodules, and bone tissue (Fig. 1).

Further histological examination of deceased material helped us to find signs of the following diseases:

- chronic myeloid leukemia (CML)
- moderate- and low-grade differentiated acinar pros-

tatic adenocarcinoma with metastasis in pelvic and paraaortic lymphatic nodules, lung parenchyma, and skeletal bones
- tertiary syphilis with granulomatous inflammation of the diaphragm and syphilitic gumma and mesaortitis
- generalized thrombotic microangiopathy was observed in the vessels of the lungs, kidneys, prostate, and spleen.

Patient G., who died during the hospital stay, had hemoblastosis and syphilis in the reported medical history. While the patient was examined doctors suspected the presence of malignancy with unknown primary localization with multiple metastatic injuries with clinical and laboratory TTP signs (hemorrhagic syndrome, thrombocytopenia, shystocytosis, and non-immune hemolytic anemia).

Despite treatment, the general patient's condition progressively worsens with increasing multiple organ decompensation signs. In the final stage of the disease course, after heart arrest and the appearance of clinical death signs CPR measures were performed according to complete guidance, but CRP had no positive effect. Biological death was constated.

From the clinician's point of view, in this case, the rapid course of the disease was caused by the onset of generalized thrombotic microangiopathy, which was a sign of probable TTP that was the cause of the appearance of multiorgan decompensation and sudden death (Fig. 2.).

Based on pathological data from the deceased patient's body we defined that the main diseases were chronic myeloid leukemia and prostatic cancer with multiple metastases. The most important complications that caused death were named such conditions: generalized thrombocytic microangiopathy and bilateral pneumonia because of malignancy intoxication which directly caused the patient's death. As an important comorbidity tertial syphilis with diaphragmed gamma and syphilitic mesaortitis.

Atypical disease courses, anemia and thrombocytopenia, kidney injury, and TTP do not allow us to manage diagnostic procedures for full vital diagnostics of prostatic malignancy with metastases. The only pathological expertise with microscopic histological examination of deceased tissues defined multiple skeletal bone, lymphatic nodular, lungs metastases with thrombosis of small vessels in lungs, kidneys, prostatic gland, and spleen.

Analyzing this clinical case, we should mention with a high level of probability that TTP was a crucial process in pathology.

The leading role in the pathogenesis of TTP was defined as a deficiency of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin-1-like domains) – metalloprotease from the family of peptidase proteins ADAM. They have a specific biological role which includes the degradation of extracellular domain transmembrane proteins. Predisposition to the occurrence of TTP is associated with pregnancy, HIV, autoimmune and inflammatory processes, transplantation, and tumors [8].

Intoxication occurs at a particular stage of the course of tumor diseases because of insufficient blood supply and oxygenation, subsequent necrosis of atypical cells and entry of decay products into the bloodstream, changes in blood rheology, and disturbances in the hemostasis system with the occurrence of thrombosis. In this case, there was thrombosis of small blood vessels, which most likely could be caused, on the one hand, by direct tumor damage to the bone marrow by atypical cells in chronic myelogenous leukemia and prostate cancer and, on the other hand, by the mediated systemic effect of tumor tissue decay products.

Another mechanism of the possible development of TTP is the inflammatory process, the sources of which in this deceased could be hematogenous metastasis and phenomena of tertiary syphilis. Another source of inflammation can be humous infiltrates of the diaphragm and mesaortitis, which existed in patient G. for many years.

TTP is based on damage to the endothelium of small vessels with subendothelial deposition of fibrin, followed by aggregation of platelets and partial or complete occlusion of vessels (thrombotic microangiopathy). First of all, the brain, kidneys, and lungs are affected. Narrowing the blood vessels' lumen contributes to the mechanical destruction of erythrocytes with the development of microangiopathic hemolytic anemia (MAHA). The fragmentation of erythrocytes characterizes it after wrapping them with fibrin threads under the influence of blood flow. The attachment of erythrocytes wrapped in fibrin threads to the endothelium of vessels occurs after the interaction of erythrocyte integrin and vascular cell adhesion molecule (VCAM-1) [9]. Another mechanism of erythrocyte attachment to vascular endothelium involves the interaction of large multimers of the Willebrand factor (Wf) as a «joint» between integrins present in the membranes of both young erythrocytes and endothelial cells.

Decreased activity of ADAMTS13 is found in disseminated intravascular coagulation syndrome (DIC), cirrhosis, uremia, acute inflammatory diseases, and in the postoperative period [10, 11].

The difficulty of diagnosing Moshkowitz's disease is explained by the absence of specific clinical symptoms in patients. The prodromal period is characterized by weakness, exhaustion, and lack of appetite. The disease develops, as a rule, acutely against the background of complete health. Often there is a prodrome resembling an acute respiratory syndrome, then a comprehensive clinic appears. Sometimes this is preceded by infectious diseases and drug intolerance. The first signs may be a

weakness, headache, dizziness, nausea, vomiting, and abdominal pain.

Classic pentad is typical for TTP [12]. It includes**:**

1) hemorrhagic syndrome (hemorrhages on the skin, nose, bleeding gums, menorrhagia, and others) on the background of thrombocytopenia (often severe with a platelet count < $30{,}0\times10^9$/l);
2) microangiopathic hemolytic anemia (MAHA), which is manifested by reticulocytosis, the presence of fragmented erythrocytes (schistocytes)) in a blood smear, hyperbilirubinemia, a negative direct antiglobulin test;
3) neurological disorders (consciousness up to coma, headache, convulsions, focal disorders (hemiplegia, visual impairment, aphasia, paresis);
4) kidney damage: microhematuria and proteinuria (most characteristic), cylindric particles in urinalysis, increased creatinine (about half of patients);
5) fever.

TTP can manifest such diseases: as pancreatitis, hepatitis, rhabdomyolysis, acute respiratory distress syndrome, myocardial infarction, nonocclusive mesenteric ischemia, peripheral ischemic syndrome, and skin gangrene. A significant part (35%) of patients with TTP develop abdominal syndrome (severe abdominal pain, nausea, vomiting) due to abdominal ischemia.

Determination of the level and activity of ADAMTS13 is not yet a routine procedure in hematological practice (in domestic laboratories the test is not performed at all) [3], that is why primary diagnostic criteria were proposed [13], the combination of which (thrombocytopenia and MAHA (dyad) in the absence of other established causes of the disease is sufficient to establish a diagnosis of TTP.

The determination of the signs of the disease that are minimally sufficient for the diagnosis of TTP led to an increase in the number of detected patients without all the signs of the classical pentad (the frequency of the occurrence of the pentad 34 – 77%). Due to this, therapy begins to shift to the first days of the disease. Patients are usually hospitalized: in the surgical department (abdominal pain with suspicion of «acute abdomen»); infectious (jaundice and fever), as well as in intensive care, neurological, therapeutic, and gynecological departments. Diagnosis of TTP, based on two criteria, requires the exclusion of diseases in which hemolytic anemia and thrombocytopenia may occur. In the presence of reticulocytosis and normocytic, laboratory doctors paid attention to the presence of schistocytes (fragmented erythrocytes).

Examination of the general blood count test and analyses of the morphology of erythrocytes, a negative direct antiglobulin test (DAT), and anamnesis allows us to quickly exclude such conditions recommended for differential diagnosis as: megaloblastic anemia, paroxysmal nocturnal hematuria malignant arterial hypertension, Evans syndrome (combination of immune thrombocytopenia and anemia), lymphoproliferative diseases.

Differential diagnoses with infectious diseases leading to bacterial septicemia or systemic inflammatory response syndrome are more complicated. Bacterial (*E. coli* 0157: H7) and viral (HIV, CMV) infection can be the cause of TTP [14, 15]. Sepsis can be manifested (especially when DIC syndrome occurs) by thrombocytopenia with a hemorrhagic syndrome, hemolysis with the presence of schistocytes and multiple organ failure. To clarify the diagnosis, it is necessary: blood cultures, search for the focus of infection, and assess the level of procalcitonin, a C-reactive protein (CRP).

Diffuse connective tissue diseases can clinically have a picture similar to TTP: thrombocytopenia, hemolysis, sometimes in combination with fever and damage to the central nervous system and kidneys. First of all, this concerns SLE, antiphospholipid syndrome [16]. SLE is characterized by: hemolytic anemia with a positive Coombs test, the presence of LE cells, and antinuclear antibodies. However, it should be remembered that TTP can be a secondary, that is, a diffuse complication of a connective tissue disease.

It is noted that diseases that occur with schistocytes and thrombocytopenia, symptoms similar to TTP can have disseminated intravascular coagulation syndrome (DIC syndrome) and hemolytic uremic syndrome (HUS also called Gasser syndrome). DIC is therefore called a syndrome that is secondary to the severe course of another, more often already established disease, and is accompanied by corresponding changes in the hemogram. HUS characterized by a combination of thrombotic microangiopathy with hemolytic anemia and acute renal failure. HUS is sometimes manifested by multiorgan pathology, including neurological complications, liver and heart injury. Clinical symptoms of HUS, significantly when the nervous system is affected, differ little from TTP, their differentiation is difficult [17]. Some experts consider TTP and HUS as one disease - TTP-HUS [18], however, with «classic» HUS, the activity of the ADAMTS13 enzyme is normal [3].

Thus, considering the criteria of the diagnostic clinical and laboratory dyad (thrombocytopenia and MAHA), the data of the pathological examination (multiple metastatic lesions, inflammatory process, tumor intoxication, thrombosis), the combination of manifestations of CML, prostate cancer with multiple metastases, tertiary syphilis served as a condition for the initiation of TTP, which was of decisive importance in the development of the patient's death.

CONCLUSIONS

TTP is life-threatening disease which does not have any specific symptoms.

In all cases of the firstly detected thrombocytopenia, it is necessary to evaluate the possibility of TTP by the pentad or dyad symptoms to decide whether it is non-immune and obligatory to focus on morphology of the erythrocytes to exclude shystocytosis.

In our case, the main reasons for the development of thrombotic icroangiopathy can be the presence of two tumor diseases - chronic myeloid leukemia and a tumor lesion of the prostate with widespread metastasis and the presence of foci of granulomatous inflammation

REFERENCES

1. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017;130(10):1181-1188. doi:10.1182/blood-2017-04-636431.
2. Greer JP et al. Wintrobe's clinical hematology. Lippincott Williams & Wilkins. 2018, p.7072.
3. Smock KJ. ADAMTS13 testing update: Focus on laboratory aspects of difficult thrombotic thrombocytopenic purpura diagnoses and effects of new therapies. Int J Lab Hematol. 2021;43 Suppl 1:103-108. doi: 10.1111/ijlh.13557.
4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi: 10.1182/asheducation-2018.1.530.
5. Rock GA, Shumak KH, Buskard NA et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991;325(6):393-397. doi:10.1056/NEJM199108083250604.
6. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354(18):1927-1935. doi:10.1056/NEJMcp053024.
7. Galstyan GM, Maschan AA, Klebanova EE et al. Lechenie priobretennoy tromboticheskoy trombotsitopenicheskoy purpuryi [Treatment of acquired thrombotic thrombocytopenic purpura]. Therapeutic archive. 2021;93(6):736-745. doi: 10.26442/00403660.2021.06.200894. (in Russian).
8. Vesely SK, George JN, Lämmle B et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood. 2003;102(1):60-68. doi:10.1182/blood-2003-01-0193.
9. Kong DH, Kim YK, Kim MR et al. Emerging Roles of Vascular Cell Adhesion Molecule-1 (VCAM-1) in Immunological Disorders and Cancer. Int J Mol Sci. 2018;19(4):1057. doi:10.3390/ijms19041057.
10. Stanley M, Killeen RB, Michalski JM. Thrombotic Thrombocytopenic Purpura. Treasure Island (FL): StatPearls Publishing. 2023. https://www.ncbi.nlm.nih.gov/books/NBK430721/ [date access 03.09.2022]
11. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. Res Pract Thromb Haemost. 2018;3(1):26-37. doi:10.1002/rth2.12160.
12. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore). 2012;91(4):195-205. doi:10.1097/MD.0b013e3182603598.
13. Downes KA, Yomtovian R, Tsai HM et al. Relapsed thrombotic thrombocytopenic purpura presenting as an acute cerebrovascular accident. J Clin Apher. 2004;19(2):86-89. doi:10.1002/jca.20007.
14. Booth KK, Terrell DR, Vesely SK et al. Systemic infections mimicking thrombotic thrombocytopenic purpura. Am J Hematol. 2011;86(9):743-751. doi:10.1002/ajh.22091.
15. Saha M, McDaniel JK, Zheng XL. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. J Thromb Haemost. 2017;15(10):1889-1900. doi:10.1111/jth.13764.
16. Fayyaz A, Igoe A, Kurien BT et al. Haematological manifestations of lupus. Lupus Sci Med. 2015;2(1):e000078. doi:10.1136/lupus-2014-000078.
17. Sheerin NS, Glover E. Haemolytic uremic syndrome: diagnosis and management. F1000Res. 2019;8:F1000 Faculty Rev-1690. doi:10.12688/f1000research.19957.1.
18. Masias C, Vasu S, Cataland SR. None of the above: thrombotic microangiopathy beyond TTP and HUS. Blood. 2017;129(21):2857-2863. doi:10.1182/blood-2016-11-743104.

ORCID and contributionship:

Halyna V. Osyodlo: 0000-0001-7563-8090 [E,F]
Svitlana A. Husieva: 0000-0002-7002-6631 [A,B,D]
Mykhailo P. Boychak: 0000-0002-8289-6239 [E,F]
Olena Antonyuk: 0000-0002-3411-196X [A,B,D-F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Olena Antonyuk
National Military Medical Clinical Centre
"Main Military Clinical Hospital"
16 Hospitalna St., 01133 Kyiv, Ukraine
e-mail: lena.nmu@gmail.com

Received: 13.02.2023
Accepted: 07.08.2023

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 the article