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**DEVELOPMENT OF LEUKEMIA AFTER COVID-19 INFECTION****Pesotskaya L.A.***c.t.s., as.prof.*

ORCID: 0000-0003-3425-6509

**Korolenko H.S.***c.t.s., as.prof.***Kravchenko A.I.***c.t.s., as.prof.*

ORCID: 0000-0003-2829-6491

**Bucharskyi O.V.***assis.*

ORCID: 0000-0003-0543-0512

**Shchukina O.S.***assis.*

ORCID: 0000-0002-9543-1545

Dnipro state medical university,

Dnipro, Vernadsky, 9, 49044

**Abstract.** *Many aspects of the COVID-19 infection, especially its complications and long-term health consequences, are still unknown. Various reactive changes in the blood test during the course of leukemia have been published. Leukocytosis [1], leukopenia [2, 3, 4], neutrophilia [5, 6], lymphocytosis and lymphocytopenia [3, 7], thrombocytopenia and, rarely, thrombocytosis [2, 8, 9] were found most often.*

*The detected changes were usually not subject to monitoring in the patient. There are reports of the diagnosis of leukemia after a recent infection with COVID-19. Therefore, studying the features of the clinical picture and hematopoiesis in such patients during the course of a viral infection, as well as in the initial manifestations of leukemia, is relevant.*

**Key words:** *COVID-19, leukemia, clinical case.*

**Introduction.**

There are numerous publications on the peculiarities of COVID-19 in different groups in terms of age, clinical manifestations, effects on different systems and organs, the effectiveness of different treatment regimens. A small number of works devoted to the analysis of changes in total blood counts infections [1, 2, 3], but in the future it is necessary to conduct basic research to study the effects of SARS CoV-2 at risk of leukemia.

There are cases of atypical COVID-19 infection with hemorrhagic syndrome and manifestations on the skin and mucous membranes, the appearance of peripheral blood (PB) and bone marrow blast cells, which are the basis for the differential diagnosis of acute leukemia [4, 5, 6].

Therefore, the clinical cases with the development of leukemia after COVID-19 infection with the study of the peculiarities of its course are noteworthy.

**Clinical cases.**

Anamnestic data of the patient. A 71-year-old woman was hospitalized in the therapeutic department of the hospital in a severe condition. Communication was difficult due to the severity of the condition. She contracted severe form of COVID-19 infection 3 months ago. The COVID-19 infection was laboratory confirmed by a



quick test for antibodies to SARS-CoV-2, as well as PCR testing on SARS-CoV-2 RNA. Patient suffered from oxygen-dependent bilateral pneumonia with respiratory failure II stage. The pneumonia was confirmed by X-ray examination. The treatment included antibacterial, anti-inflammatory, antithrombotic, symptomatic therapy and made a positive clinical and radiological dynamics. The patient was discharged in satisfactory condition. Laboratory tests at discharge are presented next. Blood test revealed mild normocytic anemia (Hb 112 g/l, er  $3.6 \times 10^{12}/l$ ), leukopenia ( $2.5 \times 10^9/l$ ), elevated ESR 60 mm/g, relative lymphocytosis (47.7%), the number of platelets within normal limits ( $234 \times 10^9/l$ ). The coagulogram revealed a slight increase in fibrinogen (5.55 g/l). Indicators of hepatic and renal functions, total protein are normal. The urine test revealed a slight proteinuria (0.053 g/l).

Patient's current clinical case. The patient's condition deteriorated two weeks before admission to the hospital, when the body temperature rose to febrile. Patient complains on cough and weakness for 6 days before hospitalization. The blood test revealed anemia (Hb 80 g/l). The general practitioner prescribed antibacterial, symptomatic treatment. Against the background of antibacterial therapy disappeared fever, but increased weakness, dizziness, decreased appetite. The day before admission to the hospital, progressive encephalopathy quickly developed, therefore the patient was urgently hospitalized.

The express test for COVID-19 is positive.

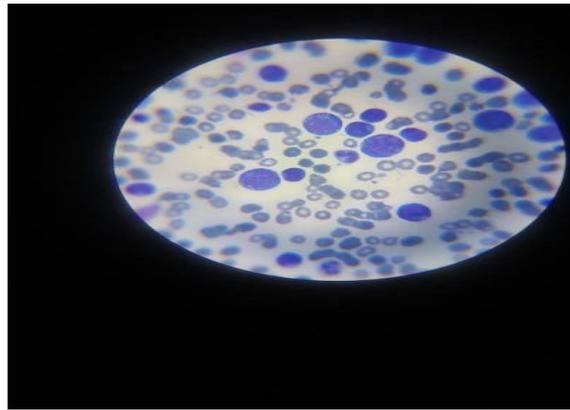
Objective data. The general condition of the patient is severe. Axillar temperature is  $37.6^{\circ}\text{C}$ . The patient has passive position. Contact is unproductive. The skin is pale. There are multiple hematoma-type hemorrhages all over the body. Lymph nodes are not enlarged. Auscultatory lungs vesicular respiration is weakened in the lower segments. Respiratory rate is 24 per minute. SpO<sub>2</sub> is 93%. Heart tones are muffled. The rhythm of the heart is regular. Heart rate is 83 per minute BP 155/80 mm Hg. The tongue is dry. The abdomen is soft and painless during palpation. Liver is not enlarged. The spleen is palpated 4 sm below the costal arch. Stool and urination are without pathology.

The results of additional research methods. Blood test: hemoglobin 69 g / l, erythrocytes  $2.2 \times 10^{12} / l$ , MCHC 377 g / l (normal up to 360 g / l), MCH 30.9 pg (within normal limits), MCV 81.9 fl (within norms), leukocytes  $80 \times 10^9 / l$ , young neutrophils 1%, band neutrophils 2%, segmental neutrophils 5%, monocytes 1%, blast cells 87%, normoblasts 4:100 leukocytes, leukolysis cells 1-2. Blast cells had morphological characteristics undifferentiated or plasmoblasts (photo 1).

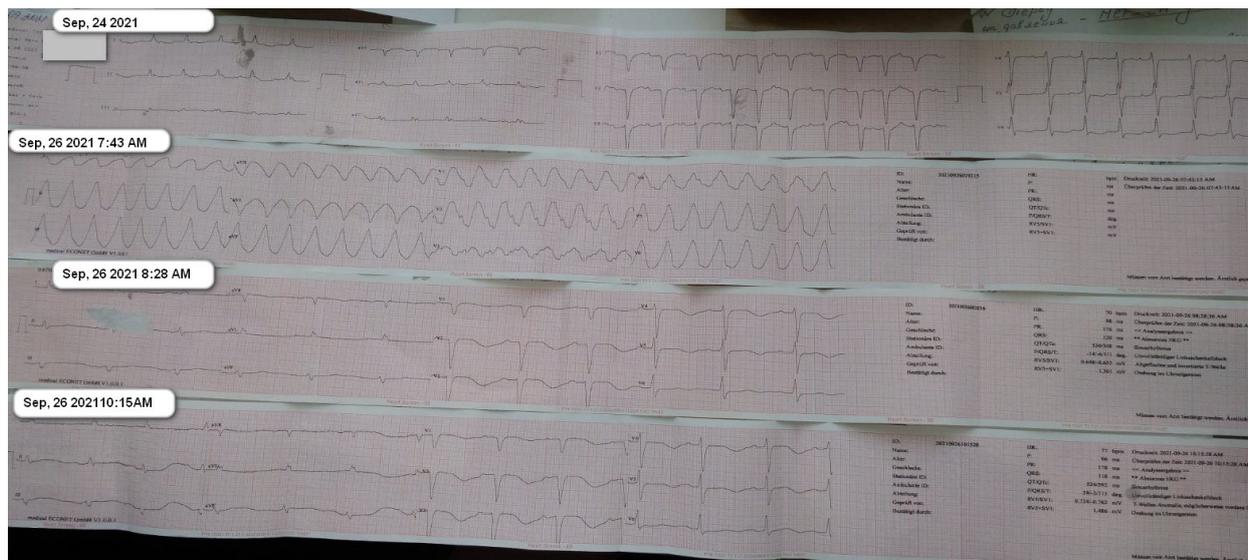
Biochemical tests: total protein 53.8 g / l, total bilirubin  $31.0 \mu\text{mol} / l$ , ALT 200 U (normal 0-32 U), AST 508.4 U (normal 0-31 U), alkaline phosphatase 357 U norm 35-104 Units), serum iron  $42.5 \mu\text{mol} / l$  (norm up to  $34.5 \mu\text{mol} / l$ ), urea 14.4 mmol / l, urea nitrogen 6.71 mmol / l, residual nitrogen  $51.4 \mu\text{mol} / l$ , creatinine 609 mmol / l.

The patient had renal and hepatic insufficiency in the background leukemic intoxication, with probability specific lesions of these organs.

ECG revealed sinus tachycardia, heart rate 102 per minute, right bundle branch block (photo 2).



**Photo 1. Smear of peripheral blood at staining on Romanovsky-Gimza,  $\times 1000$**



**Photo 2. ECG dynamics.**

CT of the chest is more consistent with bilateral interstitial pneumonia of viral etiology, CT 1, lesion 5%.

CT of the brain reveals a picture of involutive changes in the brain, periventricular leukoareosis, atherosclerosis of the internal carotid artery.

Neurologist's conclusion is mixed genesis (vascular, intoxication) discirculatory encephalopathy III stage with cognitive impairment.

The conclusion is that main disease was acute undifferentiated leukemia.

Treatment included antibacterial, anti-inflammatory (dexamethasone 8 mg IV), antihypertensive, detoxification therapy. Despite intensive care, the patient died on the first day after hospitalization.

#### Pathological and anatomical data.

According to the clinic and morphological examination, the main disease of the deceased should be considered acute blastocellular leukemia. This diagnosis was confirmed by signs of tumor lesions of the mediastinal lymph nodes, skin, liver, spleen, lungs, bone marrow and tubular bones. The smear of the native bone marrow of the femur revealed the prevalence of immature forms by type of lymphoblastic cells.



The disease was accompanied by the development of metaplastic anemia, hemorrhagic syndrome (thrombocytopenia), which led to the death.

### **Discussion.**

There are rare reports on the diagnosis of acute forms of leukemia and myelodysplastic syndrome with an excess of immature cells after a recent infection with COVID-19.

Costa BA et al. diagnosed a 35-year-old man with T-cell acute lymphoblastic leukemia (T-ALL) approximately 2 months after COVID-19 infection. Previous blood tests were within normal limits. The infection was accompanied by fever, chills, myalgia, shortness of breath for 3 days. The disease was stopped in 10 days after outpatient treatment. The first manifestations of leukemia was moderate weakness. Blood test revealed severe anemia (Hb 71 g / l), severe leukopenia (1.6 G / l), moderate thrombocytopenia (106 G / l), blasts 9%, lymphocytosis 63%. 90% of blast cells were found in the myelogram. T-ALL was determined by phenotypic studies. Leukemic lesions of the central nervous system were observed (21% of blast cells in the cerebrospinal fluid) [7].

A 36-year-old man, as in the previous case, after infection with COVID-19 after about 2 months is admitted to the hematology department. There is family ties between parents in the anamnesis. One of the sisters and four cousins had acute myeloid leukemia (AML). The patient was hospitalized for three days in hospital regarding the alleged COVID-19. A general blood test revealed mild microcytic hypochromic anemia (HB 120 g / l). The patient was discharged after the reduction of respiratory symptoms, but dry cough and fever persisted. Later, SARS-CoV-2 infection was confirmed by PCR of a nasopharyngeal sample. The blood test revealed a hemoglobin decreasing (HB 101 g / l). There was leukopenia (2.2 G / l). The myelogram revealed myelodysplastic syndrome with an excess of type 1 blasts (MDS-EB-1) was established. A bone marrow transplant was planned.

Mild symptoms of COVID-19 were observed in a 31-year-old woman approximately 3 months before hospitalization in the hematology department. During 2 weeks she suffered from increased mucus secretion, anosmia, and headache. After 8 days of treatment, PCR infection gave a negative result. The blood test was normal. Within a month before the diagnosis of hematological disease developed asthenia, fatigue, petechiae on the body, bone pain. Same as in previous cases, there were not hepatolienal and lymphadenopathy syndromes. The blood test revealed pancytopenia and blast cells. The myelogram revealed hypercellular bone marrow with dysplasia of all three lines of hematopoiesis. The diagnosis of AML, probably with previous MDS, was made. The bone marrow transplantation was planned.

The presence of malignant hematological diseases with an unfavorable prognosis is noteworthy in all cases. Anemic syndrome, thrombocytopenia of various severity, leukopenia without significant hemorrhagic syndrome, hepato-, splenomegaly, lymphadenopathy were observed in all patients at the time of disease detection. A patient with T-ALL was diagnosed with leukemic lesions of the central nervous system (21% of blast cells in the cerebrospinal fluid).

Other authors [8] cited a case of diagnosis of acute myeloid leukemia in a 61-year-old man after recovery from COVID-19 infection. Its course was severe and had



complicated by bilateral pneumothorax and pneumomediastinum. The patient was discharged in satisfactory general condition with low leukocytosis (11.6 G / l). Hemoglobin levels and platelet counts were at the lower limit of normal. After 1.5 months, acute leukemia was diagnosed with morphological characteristics of lymphoid (ALL L3) or myeloid line (AML M4, monocytic), which are prognostically unfavorable. The analysis of peripheral blood revealed normochromic microcytic anemia of mild degree in severe thrombocytopenia (26 G / l), blast-like cells, characterized by the criteria for classification of myelodysplastic/myeloproliferative disease. Bone marrow biopsy showed hypercellularity, diffuse blast infiltration, decreased megakaryocyte count. The patient was transferred to a hematology clinic.

As previous described case of T-ALL, there was damage to the nervous system, severe anemia in our case of acute lymphoblastic leukemia. But unlike the first, our patient had an instantaneous course, with a significant hemorrhagic syndrome, leukocytosis, not with leukopenia, a high percentage of ballast cells in the peripheral blood. It is probable that the aleukemic phase of acute leukemia was short in time and classical leukemic changes in morphology were already observed in the hospital. It is also noteworthy that the patient has splenomegaly, which was not in the described cases with a slower course of the disease. In general, the splenomegaly is rare in acute leukemia in adults. It can be assumed that these features are associated with the presence of re-infection and rapid progression of leukemic infiltration of internal organs, which was determined by pathological examination.

We compared the case of development of acute leukemia with signs of lymphocytic or monocytic type after COVID-19 and our case. The same in both cases was a severe course of the infection in the past, absent leukopenia, lymphocytosis, severe thrombocytopenia. In contrast, our clinical case had severe clinical anemia and significant manifestations of hemorrhagic syndrome on the skin.

Pay attention to the differences in the state of hematopoiesis after the acquisition of signs of COVID-19 infection in cases of development of acute leukemia with a slower course and in our case. Our clinical case was with instantaneous and atypical. The blood test in all these cases after infection was normal, or with mild anemia or leukocytosis. Our patient had mild anemia, an excessively elevated ESR (60 mm / h), leukopenia (2.5 G / l) with relative lymphocytosis (47.7%), a normal platelet count (234 G / l). Such indicators may be evidence of insufficiently compensated regulation of reactive changes in hematopoiesis by the virus and possibly the inflammatory process itself.

Given the combination of rapid development of cytopenia after recovery from COVID-19, the authors [7] suggest that the virus plays a role in leukemogenesis. The leading role is played by the imbalance of the renin-angiotensin system caused by SARS-CoV-2, which triggers leukemogenesis with several mechanisms. It may interact with the renin-angiotensin system (RAS), which is thought to be involved in tumor hematopoiesis [9, 10].

SARS-CoV-2 binds to angiotensin-converting enzyme (ACE2) [11]. ACE inhibitors have a protein [12] that allows the virus to enter cells in various tissues, including bone marrow [13]. This causes a decrease in the regulation of ACE inhibitors [7], which leads to the activation of immune cells and damage [14].



The formation of angiotensin-II can lead to leukemic transformation of hematopoietic cells in the bone marrow. Angiotensin-II is thought to act as an autocrine cell growth factor in acute myeloid leukemia [15]. The role of the RAS in the development of tumor growth is indicated by the results of other researchers [16 - 18]. In addition to the effects of SARS-CoV-2 on RAS, other mechanisms of potential cancer development may underlie it. In particular, COVID-19 has been associated with T-cell depletion and activation of oncogenic pathways, including JAK-STAT, MAPK and NF-kB [19, 20].

MaLauer et al. (2016) reported that the unstructured coronavirus protein (Nsp3) stabilizes factors that increase RCHY1-mediated p53 degradation associated with apoptosis [26]. The study authors noted that despite the possibility that the association between the incidence of leukemia after COVID-19 infection is random, current literature identifies a theoretically possible mechanism of association between SARS-CoV-2 infection and the development of hematological malignancies in predisposed patients [7].

An abnormal immune response to a viral infection can trigger secondary mutations, contributing to the clinical development of leukemia [22].

### Conclusions.

1. Acute leukemic process after COVID-19 infection has prognostically unfavorable morphological features.

2. Patients with a burdensome history of cancer, as well as a decrease in total quantitative indicators or percentages in the leukocyte formula in routine blood tests need dynamic control for several months until the normalization of the last ones.

### List of references

1. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. *Clin Chem Lab Med.* 2020.
2. Guan W. *et al.*, 'Clinical Characteristics of Coronavirus Disease 2019 in China', *N. Engl. J. Med.*, vol. 382, no. 18, pp. 1708–1720, Apr. 2020.
3. Wu C. *et al.*, 'Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China', *JAMA Intern. Med.*, Mar. 2020.
4. Wang D. *et al.*, 'Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.', *JAMA*, vol. 323, no. 11, p. 1061, Feb. 2020.
5. Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020 Feb 15;395(10223):507-513.
6. Qian GQ, Yang NB, Ding F, *et al.* Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series. *QJM.* 2020 Mar 17. pii: hcaa089.
7. Costa B.A., Luz C.V., Campos S.E.V., Lopez G.S., Leitao J.P.V., Duarte F.B. Can SARS-CoV-2 cause hematologic malignancies in susceptible individuals? Case series and literature review. *Hematol Transfus Cell Ther.* 2022;44:26-31.



8. Nekooghadam S.M., Moradi A., Toudeshki K. K. and Pishgahi M. A Case of Acute Leukemia Following Remission of COVID-19 Infection; an Urge to Search for a Probable Association. Arch Acad Emerg Med. 2021; 9(1): e51.
9. Lanza K., Perez L.G., Costa L.B. et al. Covid-19: the renin-angiotensin system imbalance hypothesis. Clin Sci (Lond), 134 (2020), pp. 1259-1264
10. Haznedaroglu I.C., Malkan U.Y. Local bone marrow renin-angiotensin system in the genesis of leukemia and other malignancies. Eur Rev Med Pharmacol Sci, 20 (2016), pp. 4089-4111 Medline
11. Gupta A., Madhavan M.V., Sehgal K. et al. Extrapulmonary manifestations of COVID-19. Nat Med, 26 (2020), pp. 1017-1032 <http://dx.doi.org/10.1038/s41591-020-0968-3> | Medline
12. Shang J., Ye G., Shi K. et al. Structural basis of receptor recognition by SARS-CoV-2. Nature, (2020), pp. 1-8 <http://dx.doi.org/10.1038/s41586-020-2179-y>
13. Rivellese F., Prediletto E. ACE2 at the centre of COVID-19 from paucisymptomatic infections to severe pneumonia. Autoimmun Rev, 19 (2020),
14. Cheng H., Wang Y., Wang G-Q. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J. Med Virol, (2020), pp. 0-3 <http://dx.doi.org/10.1002/jmv.25785>
15. Haznedaroglu I.C., Beyazit Y. Pathobiological aspects of the local bone marrow renin-angiotensin system: a review. J Renin Angiotensin Aldosterone Syst, 11 (2010), pp. 205-213 <http://dx.doi.org/10.1177/1470320310379876> | Medline
16. Beyazit Y., Aksu S., Haznedaroglu I.C. et al. Overexpression of the local bone marrow renin-angiotensin system in acute myeloid leukemia. J. Natl Med Assoc, 99 (2007), pp. 57-63 Medline
17. De la Iglesia Iñigo S., López-Jorge C.E., Gómez-Casares M.T. et al. Induction of apoptosis in leukemic cell lines treated with captopril, trandolapril and losartan: a new role in the treatment of leukaemia for these agents. Leuk Res, 33 (2009), pp. 810-816 <http://dx.doi.org/10.1016/j.leukres.2008.09.029> | Medline
18. Kozako T., Soeda S., Yoshimitsu M. et al. Angiotensin II type 1 receptor blocker telmisartan induces apoptosis and autophagy in adult T-cell leukemia cells. FEBS Open Bio, 13:6 (2016), pp. 442-460 <http://dx.doi.org/10.1002/2211-5463.13351> | Medline
19. Saini G., Aneja R. Cancer as a prospective sequela of long COVID-19. Bioessays, 43 (2021), <http://dx.doi.org/10.1002/bies.202100048> | Medline
20. Han H.J., Nwagwu C., Anyim O., Ekweremadu C., Kim S. COVID-19 and cancer: from basic mechanisms to vaccine development using nanotechnology. Int. Immunopharmacol, 90 (2021)
21. Ma-Lauer Y., Carbajo-Lozoya J., Hein M.Y. et al. p53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1. Proc Natl Acad Sci U S A, 113 (2016), pp. E5192-E5201. <http://dx.doi.org/10.1073/pnas.1603435113> | Medline
22. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer, 18 (2018), pp. 471-484. <http://dx.doi.org/10.1038/s41568-018-0015-6> | Medline