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Serum VEGF-A as a marker of endothelial dysfunction in children with acute lymphoblastic leukemia and pulmonary complications

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Abstract. ***Background.*** *Endothelial dysfunction (ED) is common in acute leukemia patients. The study of ED can provide more information about pathological processes in lungs of children with acute lymphoblastic leukemia (ALL). The purpose of the study is to assess the levels of vascular endothelial growth factor A (VEGF-A) and its prognostic value for pulmonary complications in children with ALL.* ***Materials and methods.*** *We examined 40 children with ALL aged 6–17 years. Group 1 included children with newly diagnosed ALL (n = 18), group 2 involved ALL survivors, who had completed the total course of chemotherapy (n = 22). The control group consisted of 15 healthy children. The level of VEGF-A in serum was assessed by enzyme-linked immunosorbent assay.* ***Results.*** *Pulmonary complications were common in the examined children with ALL, among them: acute bronchitis (23), recurrent episodes of acute bronchitis (5), pneumonia (18), wheezing (9), bronchial asthma (3), interstitial pneumonia (1), pleurisy (1), pneumothorax (3), lung fibrosis (2), respiratory failure (6). The frequency of pulmonary complications was 82.5 % during chemotherapy protocols and 20.0 % in ALL survivors after a complete course of chemotherapy. Statistically significant increase in VEGF-A level in groups 1 (180.41 (158.16; 200.00) pg/ml) and 2 (165.61 (131.65; 198.45) pg/ml) compared to controls (130.65 (129.45; 132.15) pg/ml) has been detected ($p_{1-C} = 0.000011$; $p_{2-C} = 0.007009$). There were no significant differences in VEGF-A levels between children from experimental groups ($p_{1-2} = 0.338394$). According to receiver operator characteristic (ROC) analysis, the level of VEGF-A > 198.34 pg/ml after the complete course of chemotherapy can predict the presence of pulmonary complication in ALL survivors (area under the ROC curve 0.965; sensitivity 100.00 %; specificity 89.47 %).* ***Conclusions.*** *Children with ALL have significant ED. The level of serum VEGF-A can be predictive for pulmonary complications in ALL survivors.*

Keywords: *endothelial dysfunction; vascular endothelial growth factor; pulmonary complications; leukemia; children*

Introduction

Acute lymphoblastic leukemia (ALL) occupies a leading position among all types of childhood cancer [1, 2]. Recently, there has been an improvement in the quality of treatment for this pathology [3]. However, leukemia survivors have higher mortality rates than the general population which persists for decades after diagnosis [4]. The course of the disease itself and the treatment of leukemia with the use of chemotherapeutic drugs cause serious complications and can limit the survival rates in children with ALL [5]. Hough R. and Vora A. (2017) noted that the mortality rate from complications of ALL in children and its therapy remain high and exceeds the mortality rate from relapse of leukemia [6].

According to previous studies, pulmonary complications are common in pediatric hematological malignancies [7]. Lung involvement in children with acute leukemia is typical during the acute phase of chemotherapy [5, 6]. Among the main causes of these complications, there are immunosuppression and cytopenia [8, 9], caused both by the underlying disease and myelosuppressive effects of chemotherapy, direct cytotoxic effect of drugs on lung tissue [10], blast infil-

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tration of the lungs on the background of hyperleukocytosis [11]. Among documented infection episodes, the respiratory system was the most common site [12, 13]. In addition, pulmonary complications can also occur even in the period of remission [14–16].

Up to date, endothelial dysfunction (ED) is common for patients with acute leukemia. It can be defined as inappropriate (increased or decreased) formation in the endothelium of vessels and changes in various biomarkers. In leukemic patients, endothelial cells can be affected by various damage factors, such as cytostatic agents, high-dose irradiation, hematopoietic stem cell transplantation, bacterial infections, and immune reactions [17]. Endothelial dysfunction is a common feature of various early complications of chemotherapy and can influence the prognosis of leukemia despite the optimization of treatment protocols [18–20]. Researchers of Wroclaw Medical University (2018) declare ED in childhood ALL in the acute phase by studying such biomarkers, as selectins E and P, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule 1, soluble vascular adhesion molecule 1 and vascular endothelial growth factor (VEGF) concentrations. They declare that levels of ED can be indicative of poorer short-term prognosis in children with ALL [18]. The study conducted by Hagag A.A., Abdel-Lateef A.E. et al. (2013) found increased serum thrombomodulin and von Willebrand factor levels as a marker of significant endothelial dysfunction during the acute period of ALL, which can be considered as an additional prognostic factor for unfavorable outcome in childhood ALL [19]. A study held in our institution confirmed significant ED in children with ALL by measuring nitric oxide levels and declared that the level of nitric oxide can be predictive for the development of multiple organ failure with fatal outcomes in these patients [20].

ED is present not only in the acute period of leukemia, but it is still persisting in the remission period. The study of Masopustová A., Jehlička P. et al. (2018) considers ED in ALL survivors; significantly decreased reactive hyperemia index, elevated levels of high-sensitivity C-reactive protein and E-selectin in plasma prove the presence of endothelial dysfunction in patients with ALL in remission at least 2 years after successful chemotherapy [21]. Sadurska E., Zaucha-Prazmo A. et al. (2018) detected increased circulatory levels of intercellular adhesion molecule 1 and mean carotid intima-media thickness in the remission period of ALL that demonstrates the presence of endothelial damage in blood vessels [22]. Most studies of ED in leukemic survivors deal with the relationship between endothelial damage markers and a higher risk of developing cardiovascular complications [23–25].

The barrier between air and blood consists of an alveolar epithelium (type I and type II), a continuous capillary endothelium, and connective tissue [26]. There are studies on a damage to the endothelial layer of the blood-air barrier in children with acute and chronic respiratory diseases. Several studies prove the presence of endothelial dysfunction in patients with respiratory distress syndrome and pneumonia [27, 28], and bronchial asthma [29, 30]. This indicates that the formation of chronic inflammation of the respiratory system is related to the functioning of the endothelial layer of the blood-air barrier.

However, there is a lack of studies on the status of the blood-air barrier and its endothelial layer in leukemic children. The study of ED and its damage markers can be useful for a more detailed understanding of the development of pathological processes in the lungs and its connection with pulmonary complications in children with ALL. In this study, we determined the levels of VEGF-A to find correlation with blood-air barrier damage and potential prognostic value for the formation of pulmonary complications in children with ALL.

Material and methods

General information. We examined 40 children (26 boys and 14 girls) with ALL aged 6–17 years. All patients were treated in the hematological department of the Kharkiv Municipal Clinical Children's Hospital 16 (Ukraine). The control group consisted of 15 healthy demographically matched children, who visited Kharkiv City Outpatient Hospital 16 (Ukraine) for routine health control or vaccination. None of the children in the control group had chronic respiratory diseases or any diagnosed disorders that affect endothelial function.

The inclusion criteria were verified diagnosis of ALL, age of 6–17 years, signed consent from parents, and/or patients. The exclusion criteria were refusal of the parents and/or patients to sign the consent, relapsed or secondary ALL, diagnosed chronic pulmonary diseases or disorders of endothelial function before the onset of ALL; any hereditary diseases that lead to changes in the structure or the functioning of the respiratory system, including cystic fibrosis; proven hereditary immune deficiency.

Forty examined children with ALL were divided into 2 groups: the first one included children with newly diagnosed ALL (n = 18); the second group involved ALL survivors, who had completed the total course of chemotherapy and had a remission for at least two years (n = 22). Neither patients with relapsed ALL nor with secondary ALL were included in the study due to differences in treatment protocols. To study ED in ALL patients, the level of VEGF-A was assessed. In children with newly diagnosed ALL, blood samples were collected during induction remission (protocol 1) in a period without signs of pulmonary complications and cytopenia between the 7^{th} and 14^{th} day of chemotherapy. In ALL survivors, the level of VEGF-A was evaluated during their planned visit to the hematological department for observations after a complete course of chemotherapy.

Presence of pulmonary complications in patients with newly diagnosed ALL (group 1) was reordered by clinical observation from the manifestation of the main disease till completion of the chemotherapy course. Information about the diagnosis and pulmonary complication of ALL survivors (group 2) have been received retrospectively by studying case histories.

Diagnosis and treatment of children with ALL. The diagnosis and treatment of children were carried out in accordance with the Acute Lymphoblastic Leukaemia Intensive Chemotherapy Berlin Frankfurt Munich (ALL IC-BFM) 2009 protocol [31]. The diagnosis of ALL was verified if the blast count in bone marrow was 25 % or more. Peripheral blood and bone marrow smears were evaluated according to

Table 1. General characteristics of studied patients with ALL

Parameter	Total (n = 40)	Group 1 (n = 18)	Group 2 (n = 22)
Age, Me (Lq; Uq), years	9 (7; 14)	7 (6; 15)	9.5 (7; 13)
Gender, n (%) Male Female	 26 (65.0) 14 (35.0)	 11 (61.1) 7 (38.9)	 15 (68.2) 7 (31.8)
Immunophenotype, n (%) B-lineage T-lineage	 36 (90.0) 4 (10.0)	 15 (83.3) 3 (16.7)	 21 (95.5) 1 (4.5)
FAB classification, n (%) L1 L2	 31 (77.5) 9 (22.5)	 11 (61.1) 7 (38.9)	 20 (90.9) 2 (9.1)
Risk group, n (%) Standard High	 29 (72.5) 11 (27.5)	 12 (66.7) 6 (33.3)	 17 (77.3) 5 (22.7)

French-American-British criteria; immunophenotyping, and chromosomal analyses were performed. Patients were classified into risk groups according to the ALL IC-BFM 2009 protocol. Independently of risk group, all children with ALL started treatment with induction (protocol I, phase A and phase B) with the only difference of a doubled dose of daunorubicin in intermediate- and high-risk groups of patients. Then the therapy is followed by consolidation (protocol M) for the low- and intermediate-risk children or by the HR protocol for children with high risk. After that re-induction (protocol II, phase 1 and phase 2) was used in all the ALL children independently of the baseline risk. Maintenance treatment is started 14 days after the end of re-induction.

Assessment of VEGF-A in serum. Venous blood (4 ml) was taken in the morning in the fasting state, and centrifuged at 2,300 g for 10 min. After that serum samples were immediately frozen at –20 °C until assays. VEGF-A levels in the exhaled breath condensate were analyzed by the enzyme-linked immunosorbent assay using commercial kits (Human VEGF-A, eBioscience (Bender MedSystems), catalog number: BMS277, USA) according to the manufacturer's instructions.

Statistical analysis. For statistical analyses of data, Statistica 8 (Tulsa, OK, USA) has been used. Shapiro-Wilk test has been applied for verification of the distribution according to the Gauss law. Given the fact that the samples had a non-normal distribution, the median (Me), and interquartile range (Lq — lower quartile; Uq — upper quartile) were determined for the statistical analysis. To compare two independent samples, a non-parametric Mann-Whitney U-test has been used. The difference in the parameters has been considered significant at $p < 0.05$. Receiver operating characteristic (ROC) curves were drawn for variables to determine the optimal cut-off values to predict an endpoint.

Ethics approval and consent to participate. Each study participant and his/her parents were informed about the nature of the study. Informed consent for participation in the study was obtained from the parents of all patients and from patients aged 14–18. The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University, Ukraine (Protocol No. 8 dated October 5, 2016) and was conducted according to the Declaration of Helsinki 1975.

Results

Forty children with ALL took part in this study. General characteristics of patients are highlighted in Table 1. There was a significant prevalence of boys over girls ($p = 0.0385$). Patients age was from 6 to 17 years. All the patients were Caucasians.

Bone marrow examination detected that B-cell lineage ALL was prevalent ($p = 0.0002$) and most children had the standard risk group ($p = 0.067$). In group 1, two children die due to the progression of the underlying disease.

We recorded pulmonary complications that occur in different periods of ALL in children of both groups. Some patients had more than one lung complication. The frequency of detected pulmonary complications is presented in Table 2.

It was found that pulmonary complications were common and presented in 82.5 % of the children with ALL during different periods of the disease. The most frequent complications were acute bronchitis (57.5 %), pneumonia (45.0 %), and wheezing (22.5 %). Among 23 children with acute bronchitis, 5 had recurrent episodes. Pneumonias

Table 2. Pulmonary complications in children with ALL

Complications	Total (40 patients)	
	n	%
Acute bronchitis	23	57.5
Recurrent episodes of acute bronchitis	5	12.5
Wheezing	9	22.5
Bronchial asthma	3	7.5
Pneumonia	18	45.0
Interstitial pneumonia	1	2.5
Pleurisy	1	2.5
Pneumothorax	3	7.5
Lung fibrosis	2	5.0
Respiratory failure	6	15.0
Total	33	82.5

were complicated by pleurisy in 1 case, and by pneumothorax in 3 cases. Also, there was one case of interstitial pneumonia. Respiratory failure was present in 6 patients. Among 9 children with wheezing, bronchial asthma was diagnosed in 3 cases. None of these children had wheezing episodes before the onset of ALL.

Acute complications were common when using chemotherapy protocols ALL IC-BFM 2009 and presented in 82.5 % of patients. The frequency of most common complications and their distribution according to the treatment protocols are presented in Fig. 1.

Some ALL survivors in remission, even after a complete course of chemotherapy protocols, still had respiratory complaints. The frequency of pulmonary complications was 20.0 % in all examined children after a completed course of chemotherapy. These complications included 2 cases of lung fibrosis, 3 cases of bronchial asthma, and 3 cases of recurrent episodes of acute bronchitis.

According to obtained results, a statistically significant increase in VEGF-A level in group 1 (180.41 (158.16; 200.00) pg/ml) and group 2 (165.61 (131.65; 198.45) pg/ml) compared with the control group (130.65 (129.45; 132.15) pg/ml) has been detected ($p_{1\text{-}C}$ = 0.000011; p = 0.007009). There were no significant differences in VEGF-A between groups 1 and 2 (p_{1-2} = 0.338394). Therefore, in children with ALL in remission, even after the complete course of chemotherapy, the increased level of VEGF-A is still persisting.

We have not found any significant difference in VEGF-A levels in patients of the group 1 with and without pulmonary complications during the acute phase of chemotherapy (p = 0.470588). Among ALL survivors in the group 2, children with persistent pulmonary complications had significantly higher levels of VEGF-A (p = 0.005195). To study the relationship between levels of VEGF-A and the formation of lung complications in the intense phase of chemotherapy and in ALL survivors, we performed ROC-analyses.

ROC-analysis demonstrates the lack of ability to predict acute pulmonary complications during chemotherapy in the group 1. According to the conducted ROC-analyses (Fig. 2), the level of VEGF-A > 198.34 pg/ml in samples collected after the completion of chemotherapy protocols can predict the presence of pulmonary complication in ALL survivors (AUC 0.965; sensitivity 100.00 % (95% CI 29.2–100.0); specificity 89.47 % (95% CI 66.9–98.7); +LR 9.50; –LR 0.00).

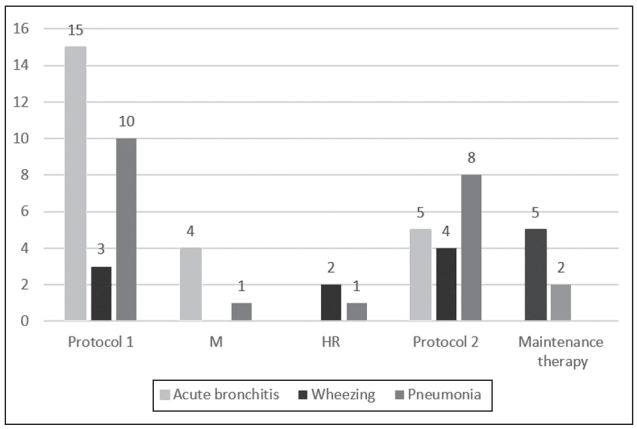

Figure 1. Most common pulmonary complications in children with ALL (n = 40) in different stages of ALL IC-BFM 2009 protocol, which consists of induction (protocol I), consolidation (protocol M for standard risk group, HR for high risk group), re-induction (protocol 2) periods and maintenance treatment

Discussion

Since ALL was firstly described in children in the 1920s, the prognosis has improved from a totally fatal disease to one with event-free survival rates of 73–87 % in a 5-year period [3, 6]. However, despite the success in the treatment of leukemia, its complication is still a significant problem in hematological practice [5, 6]. Therefore, more and more studies deal with complications of acute leukemia. Our study is focused on pulmonary complications of ALL in children.

Based on the dynamic management and analysis of medical documents, the prevalence of clinically significant pulmonary complications was confirmed. Their frequency was 82.5 % that is higher than in other studies [7, 10]. Most of these complications manifested in the acute phase of chemotherapy protocol, which corresponds to literature data [10, 12, 13].

Acute bronchitis, pneumonia, interstitial pneumonia, wheezing episodes, the formation of asthma, pleurisy, and pneumothorax were noted among the complications we identified. Most of them are triggered by infections. These statistics corresponds to the literature data. Erdur B., Yilmaz S. et al. (2008) noted that infectious lesions were the most frequent pulmonary complications — 92.4 % [32].

The prevalence of delayed pulmonary complications of varying severity in pediatric convalescents of cancers according to previous studies ranges from 45.5 to 84.1 %, among them only 8 % are clinically detected [16, 33]. Ac-

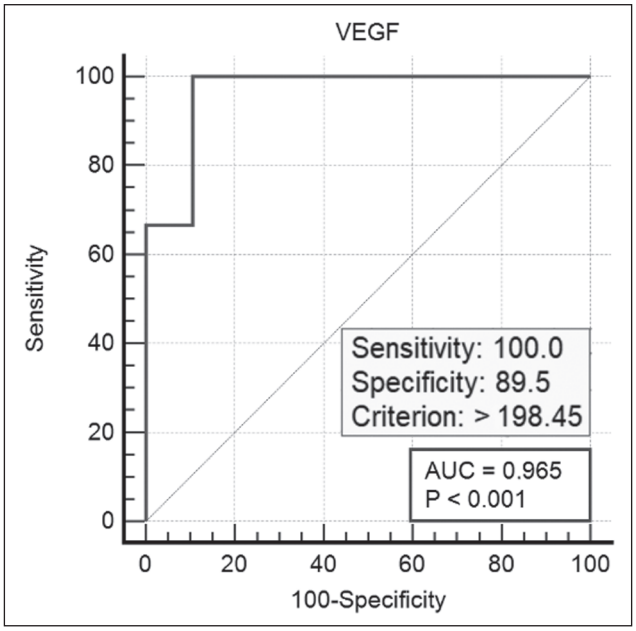

Figure 2. ROC-curve for predicting the presence of pulmonary complications in ALL survivors by VEGF-A level in serum collected after completed course of chemotherapy

cording to our data, pulmonary complications were present in 20.0 % convalescent children after completing the course of protocol chemotherapy. Differences in this frequency can be explained by patient samples. Both mentioned studies assess the level of lung complications in all types of childhood cancer survivors, while our study concerns only pediatric leukemia cases.

Previous studies confirm that ED is a typical pathological process in children with ALL both in the acute phase of the disease [18–20] and during remission [21–25]. The results of our study and detected increased levels of VEGF-A in children with ALL compared to controls support a hypothesis of the existence of endothelial dysfunction during chemotherapy and the remission period.

The vascular endothelial growth factor is considered the ED marker and the main factor of normal and pathological angiogenesis. Its high secretion can be induced by hypoxia, endothelial cell injury and is typical for cancer, diabetes, macular degeneration, and other pathological conditions [34]. It should be noted that VEGF level depends on platelet count [35]. Therefore, we collected clinical material (blood serum) during a period without thrombocytopenia to exclude possible differences in the level of VEGF-A due to this factor.

Up to date, there are several studies that consider a damage to the endothelial layer of the blood-air barrier in children and respiratory diseases such as respiratory distress syndrome, pneumonia [27, 28], and bronchial asthma [29, 30]. However, there is a lack of research on the relationship between ED and lung involvement in children with acute leukemia.

In contrast to previous studies, we firstly assess endothelial dysfunction and its relation to pulmonary complications in different periods of pediatric ALL. The combination of high levels of damage marker VEGF-A and high incidence of pulmonary complications in ALL children allows us to suggest the relationship between the dysfunction of the endothelial layer of the blood-air barrier and the formation of chronic inflammation process in the lungs. Our study and conducted statistical analyses revealed that the level of VEGF-A can be predictive for delayed pulmonary complications in ALL survivors.

Our study has several limitations. We could not detect whether recorded pulmonary complications are associated with the course of underlying disease or toxic effects of cytostatic therapy, because these factors influence at the same period of time and most of them are not specific. Another limitation is a small sample of patients, due to the fact that acute leukemia is a comparatively rare disease. Additionally, as our study sample included only Caucasians, our results may not be generalizable to other ethnic groups. Therefore, further research with larger samples, including multicentral ones, can be useful for a more in-depth study of the problem.

Conclusions

Children with ALL have significantly increased levels of VEGF-A and a high incidence of lung complications (82.5 %). Even during remission, the damage marker of endothelial dysfunction is increased. Serum concentration of VEGF-A above 198.34 pg/ml after the total course of chemotherapy can be predictive for pulmonary complications in ALL survivors with a sensitivity 100 % and a specificity 89.5 %.

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VEGF-A як маркер ендотеліальної дисфункції в дітей із гострою лімфобластною лейкемією та легеневими ускладненнями

Резюме. Актуальність. Ендотеліальна дисфункція (ЕД) є характерним патологічним станом у пацієнтів із гострою лейкемією. Оцінка стану ЕД має значення для більш детального розуміння патологічних процесів у легенях дітей із гострою лімфобластною лейкемією (ГЛЛ). **Мета:** оцінити рівні судинного ендотеліального фактора росту А (VEGF-A) у сироватці крові та його прогностичне значення щодо легеневих ускладнень у дітей із ГЛЛ. **Матеріали та методи.** Обстежено 40 пацієнтів із ГЛЛ віком 6–17 років. Перша група включала дітей з уперше діагностованою ГЛЛ (n = 18), до 2-ї увійшли пацієнти з ГЛЛ, які закінчили повний курс хіміотерапії (n = 22). Контрольну групу становили 15 здорових дітей. Рівень VEGF-A оцінювали методом імуноферментного аналізу. **Результати.** В обстежених дітей із ГЛЛ були поширеними легеневі ускладнення: гострий бронхіт (23), повторні епізоди гострого бронхіту (5), пневмонія (18), обструктивний бронхіт (9), бронхіальна астма (3), інтерстиціальна пневмонія (1), плеврит (1), пневмоторакс (3), фіброз легень (2), дихальна недостатність (6). Частота легеневих ускладнень становила 82,5 % під час хіміотерапії та 20,0 % у період ремісії після повного курсу хіміотерапії. Виявлено статистично вірогідне підвищення рівня VEGF-A в 1-й (180,41 (158,16; 200,00) пг/мл) та 2-й групах (165,61 (131,65; 198,45) пг/мл) порівняно з контрольною (130,65 (129,45; 132,15) пг/мл) ($p_{1\text{-}К}$ = 0,000011; $p_{2\text{-}К}$= 0,007009). Вірогідних відмінностей у рівнях VEGF-A між 1-ю та 2-ю групами не визначено ($p_{1–2}$ = 0,338394). За даними проведеного ROC-аналізу, рівень VEGF-A > 198,34 пг/мл після повного завершення курсу хіміотерапії прогностично значущий щодо формування легеневих ускладнень у дітей із ГЛЛ у тривалій ремісії (AUC 0,965; чутливість 100,00 %; специфічність 89,47 %). **Висновки.** Діти з ГЛЛ мають значну ЕД. Рівень сироваткового VEGF-A може бути прогностичним фактором щодо розвитку легеневих ускладнень у дітей у період ремісії ГЛЛ після завершення повного курсу хіміотерапії.

Ключові слова: ендотеліальна дисфункція; судинний ендотеліальний фактор росту; легеневі ускладнення; лейкемія; діти