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PULMONARY COMORBIDITY IN CHRONIC LYMPHOPROLIFERATIVE DISEASES: REALITIES OF THE PROBLEM IN THE DNIPRO REGION

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Ключевые слова: *лимфопролиферативные заболевания, лимфома, респираторные заболевания, одышка*

Abstract. Pulmonary comorbidity in chronic lymphoproliferative diseases: realities of the problem in the Dnipro region. Gashynova K.Yu., Usenko G.V. *The prevalence of the chronic lymphoproliferative diseases is increasing worldwide with increase of the population age. It is known that the presence of comorbidities in such patients plays an important role in predicting treatment outcomes. The aim of the work was to study the prevalence and determine the structure of respiratory symptoms and comorbid pulmonary pathology in patients with chronic lymphoproliferative diseases (CLPD) in the Dnipro region of Ukraine. After analyzing 986 cards of inpatients of the hematology department, whose average age was 65 (56; 69) years, it was determined that 9.0% of patients had at least one chronic respiratory disease, the most common among which were chronic bronchitis, chronic obstructive pulmonary disease, as well as community-acquired pneumonia. Dyspnea and tachypnea are also common among patients with CLPD without established respiratory comorbidity, cardiovascular disease, or anemia. Based on the data obtained, we can recommend a study of the respiratory function and pulse oximetry, as well as a thorough collection of anamnesis of smoking and analysis of the results of chest computed tomography in all patients with CLPD in order to identify the possible cause of shortness of breath and establish the presence of respiratory comorbidity.*

Реферат. Сопутствующая легочная патология при хронических лимфопролиферативных заболеваниях: реалии проблемы в Днепропетровском регионе. Гашинова Е.Ю., Усенко А.В. *Распространенность хронических лимфопролиферативных заболеваний увеличивается во всем мире и растет вместе с возрастом населения. Известно, что наличие сопутствующей патологии у таких пациентов играет важную роль в прогнозировании результатов лечения. Целью работы было изучение распространенности и определение структуры респираторных симптомов и коморбидной легочной патологии у пациентов с хронической лимфопролиферативной патологией (ХЛПП) Днепропетровского региона Украины. Проанализировано 986 карт стационарных больных гематологического отделения, средний возраст которых составлял 65 (56;69) лет, определили, что 9,0% пациентов имели хотя бы одно хроническое заболевание дыхательной системы, наиболее распространенными среди которых были хронический бронхит, хроническое обструктивное заболевание легких, а также внегоспитальная пневмония. Одышка и тахипное также часто встречаются среди больных с ХЛПП без установленной респираторной коморбидности, патологии сердечно-сосудистой системы или анемии. На основании полученных данных мы можем рекомендовать исследование функции внешнего дыхания и проведение пульсоксиметрии, а также тщательный сбор анамнеза курения и анализ результатов компьютерной томографии органов грудной клетки у всех больных с ХЛПП с целью идентификации возможной причины одышки и установления наличия респираторной коморбидности.*

Chronic lymphoproliferative diseases (CLPD) belong to the group of pathological conditions of the so-called multifactorial genesis, in the development

of which environmental and genetic factors play a role [5]. Chronic lymphocytic leukemia (CLL) is one of the most common CLPD. The incidence rate

worldwide is up to five cases per 100,000 population and is higher in men. Multiple myeloma (MM), which is more common in the elderly, is the second most common oncohematological pathology – in European countries about four cases per 100,000 [10]. Lymphomas, which have different prevalences depending on the pathomorphological variant, age and sex, are also common among CLPD. For example, the prevalence of non-Hodgkin's lymphoma in the United States is 19.7 per 100,000 population, increasing exponentially with age (9.3 per 100,000 under the age of 65 and 91.5 per 100,000 over the age of 65) and doubling more often in men (23.9 per 100,000) than in women (16.4 per 100,000 population) [15].

It is now known that the presence of comorbidities plays an important role in predicting the outcome of CLPD treatment, especially in patients older than 75 years [6], so the presence of comorbid conditions and correction of treatment tactics for comorbidities may be one of the key aspects of successful therapy. However, publications on this subject have begun to appear for the most part only in the last decade.

Thus, according to a study conducted at the Mayo Clinic (USA) and published in 2017 [14], the most common comorbidities in patients with CLL were rheumatic diseases (42%), dyslipidemia (41%) and hypertension (40%). However, respiratory pathology also played an important role: among all patients with CLL, 17% had respiratory diseases and among patients with CLL who died, 23% had respiratory comorbidity. Thus, the presence of respiratory pathology may be a potential risk factor for an unfavorable prognosis for this category of patients. Another study found that a significant proportion of patients with CLL have concomitant lesions of the cardiovascular system (33%) and metabolic disorders (26%), while the proportion of comorbid respiratory diseases is only 5% [13]. Another study found that more than a quarter of patients with MM (27%) had respiratory disease, but data on the impact of such comorbidity on the course of the disease in the work were absent [2]. However, according to some publications, the share of concomitant respiratory diseases in CLPD is less than one percent or such pathology is not described at all [12].

Based on the fact that in 25% of cases CLPD is accompanied by an increase in mediastinal lymph nodes [15], which can potentially cause narrowing of the airways, correlation of the degree of bronchial obstruction with the probability and severity of adverse events in these diseases generates interest. However, currently spirometry is not included in the diagnostic standards in this category of patients.

Because patients with CLPD receive therapy, including drugs that have immunosuppressive activity such as cytostatics, infections, including those localized in the respiratory system occupy the leading position as for the complications. Life-threatening infectious events due to malignancies and treatment-related immunosuppression are important causes of death in hematological cancer [7, 8, 9, 13]. Invasive mold infections are the most common cause of serious, often life-threatening infections in patients with neutropenia that persists for more than two weeks [3], so they need special attention from clinicians and scientists.

Thus, the literature data on the prevalence of comorbid respiratory pathology in CLPD are contradictory and limited, and data on the impact of concomitant respiratory pathology on the prognosis of these diseases are very limited. Therefore, despite the rapid development of research on CLPD, the prevalence and clinical significance of respiratory comorbidity remains open both in Ukraine and worldwide.

The aim of the study was to study the prevalence and determine the structure of respiratory symptoms and comorbid pulmonary pathology in patients with lymphoproliferative diseases in the Dniepro region of Ukraine.

MATERIALS AND METHODS OF RESEARCH

The retrospective clinical study [3] included medical records of inpatients who were hospitalized in 2018-2019 in the hematology department of the Municipal Non-Profit Enterprise "City Clinical Hospital No. 4" Dnipropetrovsk City Council" with a confirmed clinical diagnosis of CLPD. Complaints, life and medical history, physical data, smoking status, computed tomography (CT) of the chest, and full blood count tests were evaluated.

The study was conducted in accordance with the principles of bioethics set out in the Declaration of Helsinki on Ethical Principles for Human Health Research and the Universal Declaration on Bioethics and Human Rights (UNESCO).

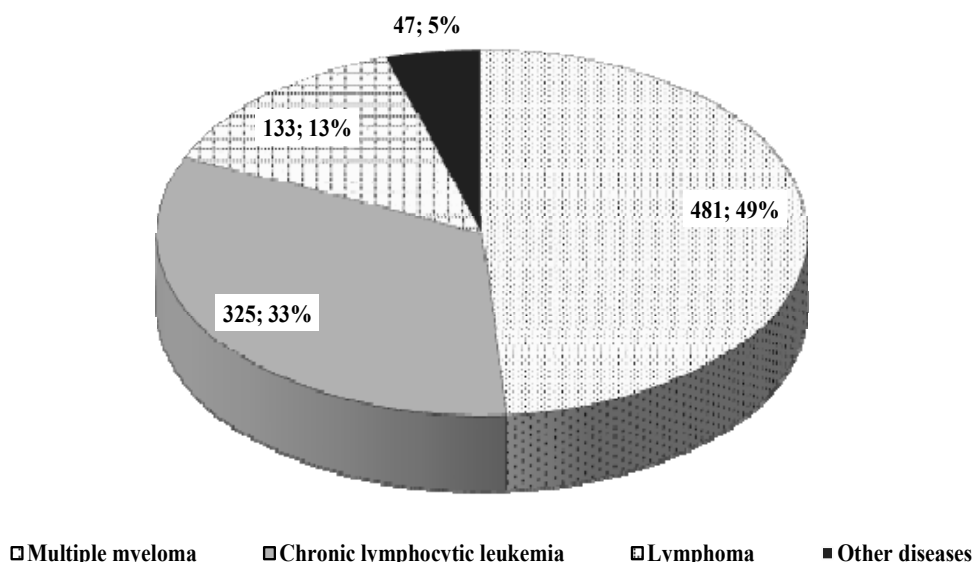
Statistical analysis was performed in Excel AtteStat 2010 (license number 02260-018-0000106-48794). Quantitative variables were presented as the mean value (standard deviation, SD) with the correct data distribution or as the median (quarter-quarter scale) with the wrong distribution. Qualitative variables are presented as absolute numbers and percentages (n, %). The distribution of variables was analyzed using the Shapiro-Francia test. The Chi-square test was used to compare two independent binary samples. Student's t-test with the correct distribution and Wilcoxon's test with the wrong distribution were used to compare the two independent

samples with quantitative data. The 95% confidence interval was calculated for the independent variables, with $p \leq 0.05$ considered significant [1].

RESULTS AND DISCUSSION

The retrospective clinical study included 986 inpatient medical records (511 (51.8%) of them

belonged to men). The average age of hospitalized was 65 (56; 69) years, the average duration of hospitalization was 9 (6; 13) days, mortality – 2.4%. The structure of the main clinical diagnoses in the medical records selected for analysis is presented in the Figure.



Structure of clinical diagnoses of hospitalized CLP patients

As can be seen from the Figure, the majority of those hospitalized were patients with MM and CLL. According to medical records, a total of 135 cases (13.7%) of hospitalized patients with CLP had at least one respiratory disease. The proportion of patients with comorbid pulmonary pathology did not differ significantly in groups with different basic diagnoses, being 11% in MM (53 patients), 15.4% – in CLL (50 patients), 18% – in patients with lymphoma (24 people) and 8.5% – in other diseases (4 people).

It should be noted that the vast majority of cases of pulmonary pathology – 59 (43.7% of respiratory diseases and 6% of all medical records) were community-acquired pneumonia. However, in 89 cases (65.9% and 9.0%), at least one chronic disease of the respiratory system respectively, was registered. The most common were: chronic bronchitis – 50 cases (37.0% and 5.1%), chronic obstructive pulmonary disease – 18 cases (13.3% and 1.9%), pathology of the upper respiratory tract – 14 cases (10.4% and 1.4%), tracheitis – 4 cases (3.0% and 0.4%), bronchial asthma – 3 (2.2% and 0.3%).

In the analysis of disorders of the respiratory system, it was found that according to all medical records the most common complaint was shortness of breath – 136 cases (14.1%). Cough was registered in 55 (5.6%) cards, tachypnea – in 20 (2.1%). However, it was noteworthy that the signs that may be associated with respiratory pathology were found not only in patients with concomitant respiratory diseases. To clarify this issue, we divided all the analyzed cases into two groups: group 1 included patients with established respiratory pathology (n=135, 13.7%), group 2 – patients without documented respiratory diseases (n=851, 86.3%). The groups were compared by sex ($p=0.23$ by the Chi-square criterion), but a statistically significant difference was found by age ($p=0.02$ by the Wilcoxon test). The average age of patients in group 1 was 66 (56; 72) years, in group 2 – 65 (56; 69) years. It was not possible to assess the smoking status due to the lack of relevant information in the medical records.

The frequency of respiratory symptoms in the comparison groups is shown in the table.

**Frequency of respiratory symptoms in hospitalized patients
with CLPD depending on the presence of respiratory pathology**

Sign, units of measurement	Group 1 (n=135)	Group 2 (n=851)	p
Shortness of breath, n (%)	27 (20)	116 (13.6)	0.13
Unproductive cough, n (%)	9 (6.7)	12 (1.4)	0.0006
Productive cough, n (%)	10 (7.4)	24 (2.8)	0.03
Tachypnea (> 20/min.), n (%)	3 (2.2)	17 (1.9)	0.24

It was found that cough was more common in the group of patients with respiratory pathology. However, the difference in the proportion of patients with dyspnea and tachypnea was statistically insignificant between the groups. Moreover, in chronic respiratory diseases, dyspnea occurred significantly ($p < 0.001$) more often (35.0%) than in patients with pneumonia (23.7%). Because shortness of breath is often a sign not only of respiratory pathology, but also of cardiovascular system (CVS) and anemia, we also analyzed whether there is a difference between the proportion of patients with a history of such diseases among patients of both groups. It was found that patients with established respiratory pathology were statistically significantly more likely to have pathology of CVS (9 (6.7%) and 12 (1.4%), respectively) ($p = 0.0006$). Patients with a history of CVS diseases (62; 14.6%) and without it (81; 15.3%) did not differ significantly ($p = 0.94$). 88 (65.2%) and 484 (56.9%), respectively ($p = 0.034$). Thus, according to the obtained data, the presence of tachypnea and dyspnea in patients with CLPD without documented respiratory pathology can not be explained by anemia or pathology of CVS.

The conclusion on the results of CT of the chest was available in 526 (53.3%) medical records. However, it was not possible to assess the effect of changes of the chest on on CT considering prevalence of dyspnea and tachypnea in patients without respiratory pathology due to a very brief

description of the results of the study. Routine measurement of oxygen saturation and spirometry in patients with CLPD was not performed.

CONCLUSIONS

1. The study showed that in the Dnipro region among patients who were hospitalized in the hematology department, 9.0% had at least one chronic disease of the respiratory system. The most common were chronic bronchitis (5.1%) and chronic obstructive pulmonary disease (1.9%). Community-acquired pneumonia was recorded in 6% of all medical records.

2. Respiratory symptoms occur in a large number of patients with chronic lymphoproliferative diseases without concomitant respiratory pathology. Moreover, dyspnea and tachypnea in such patients cannot be explained by the presence of concomitant pathology of CVS or anemia.

3. Such data may be the basis for the recommendation of the study of external respiratory function and measurement of oxygen saturation in all patients with chronic lymphoproliferative diseases in order to identify the possible cause of shortness of breath. Also in such patients it is advisable to more carefully collect a history of smoking, as well as a detailed analysis of the results of computed tomography of the chest.

Conflict of interest. The authors declare no conflict of interest.

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