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HEMOGLOBIN LEVELS AS A COMPONENT OF THE PARANEOPLASTIC SYNDROME IN LUNG CANCER

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Summary: Recently, some studies indicate that paraneoplastic syndrome may be the first sign of lung cancer and may serve in early detection of cancer. Namely, during the last ten years, an increasing importance is given to hematological paraneoplastic syndrome of lung cancer. The aim of this study was to evaluate whether hemoglobin levels have paraneoplastic nature in patients diagnosed with lung cancer prior to any form of therapy, and to examine its relationships with platelet count.

The study included 239 patients with lung cancer who were hospitalized at the Clinic for Pulmonary Diseases, Clinical Center of Sarajevo, during the period from January 2005 to December 2008, and a control group of 60 healthy persons. The study did not include lung cancer patients with evident hemoptysis and patients who were under chemotherapy and/or were undergoing surgery.

The results of our study have shown that the average hemoglobin for each histopathological type of lung cancer was significantly lower than the average hemoglobin in control group, except for large cell carcinoma. Lung cancers are classified according to the TNM classification. There were no significant differences in average hemoglobin between different stage of non small cell lung carcinoma as well as in average hemoglobin between limited and extended stage of small cell lung carcinoma.

Our results also showed that there was a significant negative correlation between platelet count and hemoglobin levels.

On the basis of our results we concluded that low hemoglobin in patients with lung cancer, with no evident hemoptysis, may have the character of paraneoplastic syndrome.

Key words: hemoglobin concentration, lung cancer, thrombocytosis.

INTRODUCTION

Paraneoplastic syndromes are common in patients with lung carcinoma. Paraneoplastic syndromes may be the initial presentation even before the manifestation of the lung carcinoma (1, 2).

Numerous studies (1, 2, 3, 4) suggest that thrombocytosis should be analyzed in correlation with other analysis of the blood, such as erythrocyte sedimentation rate, hemoglobin and white blood cells count. The authors believe that this analyses are cheap screening tests, that have features of paraneoplastic syndromes and may help in distinguishing benign from malignant lesion in the lung (2, 5). This particularly applies to those changes in the lung that according to history of disease and X-ray analysis was not possible to differentiate benign from malignant lesions. Specifically, the authors argue that before an expensive and aggressive search, should be taken into consideration and the above analysis of blood.

The aim of this study was to evaluate whether hemoglobin levels have paraneoplastic nature in patients diagnosed with lung cancer, before to any form of therapy, chemotherapy and/or surgery, and to examine its relationships with platelet counts.

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MATERIAL AND METHODS

The study included a study group of 239 patients with a confirmed diagnosis of lung cancer before any form of therapy and without significant hemoptysis, who were hospitalized at the Clinic for Pulmonary Diseases, Clinical Center of Sarajevo, during the period from January 2005 to December 2008, and a control group consisted of 60 age- and sex- matched healthy persons.

The study did not include lung cancer patients present with: inflammatory-disease, autoimmune disease, other malignancy with marked hemoptysis.

In this study, were not included, lung cancer patients who are under chemotherapy and/or are subjected to surgical intervention. Data, that included lung cancer histological type and lung cancer stage, age, gender, platelet count and hemoglobin values were taken from medical history.

The preoperative white blood cell count, hemoglobin (Hb) level and platelet count were obtained before the surgical procedure. Anaemia was defined as Hb level < 130g/L in men and < 120g/L in women, and thrombocytosis as a platelet count > 400 x 10⁹/L. Clinical staging was based on bronchoscopy, computed tomography of the chest, abdomen and brain, and bone scintigraphy. Classification according to the histological type was made according to World Health Organisation (WHO)/International Association for the Study of Lung Cancer (IASLC) criterias, and the Tumor, Node and Metastasis (TNM) classification was made according to the seventh edition of the "TNM classification of malignant tumours" (6, 7).

The protocol was approved by the Ethics Committee of the institution.

In statistical analysis data were analysed using SPSS, version 13.0. Data were analysed descriptively

and expressed as raw frequencies and percentages, ANOVA test, and 95% confidence intervals (95% CI) were calculated with confidens interval analysis (CIA). For each continuous variable to calculate basic statistical indicators univariate analysis. The significance level was set at $p < 0.05$. Pearson's test was used to calculate the correlation coefficient r between two variables, thrombocytosis and hemoglobin values.

RESULTS

The study group consisted of 239 patients with a confirmed diagnosis of lung cancer before any form of therapy and without significant hemoptysis. The average age was 63.4. The youngest patient was 24 years and the oldest 86 years old. The ratio of men to women patients was 3.2 : 1. The control group consisted of 60 age- and sex- matched healthy persons.

Significant difference was found in hemoglobin level in each histological type of lung carcinoma compared to control group ($p < 0.05$), except for large cell carcinoma ($p > 0.05$) (Table 1).

No significant difference ($p > 0.05$) in hemoglobin levels between NSCLC subtypes was found (Table 2).

No significant difference in hemoglobin levels between limited and extended stage of small cell lung carcinoma ($p > 0.05$) was found (Table 3).

No statistically significant difference in hemoglobin levels between earlier stage (I, II) and advanced stage of NSCLC (III and IV) was found ($p > 0.05$) (Table 4).

No statistically significant difference in hemoglobin levels between NSCLC and SCLC was found ($p > 0.05$), as is shown in Table 5.

A negative correlation was found between hemoglobin levels and platelet count in patients with lung cancer ($r = -0.87$, $p < 0.05$) (Figure 1).

Patients	Xmin	Xmax	Mean X	CI*, 95%	Standard deviation (+/-)	Median	Significance
Adenocarcinoma	111	160	121	117-124	20.6	122	p < 0.05
control group	104	166	140	135-144	10.7	140	
Squamous cell carcinoma	85	179	125	121-128	20.8	121	p < 0.05
control group	104	166	140	136-144	10.7	140	
Large cell carcinoma	133	136	134	122-146	1.5	134	p > 0.05
control group	104	166	140	137-142	10.5	140	
Small cell carcinoma	94	158	126	122-130	15.7	130	p < 0.05
control group	104	166	140	137-143	10.7	140	

Legend: hemoglobin* = hemoglobin g/L; CI* = confidence interval

Table 1. Analysis of hemoglobin* levels in specific histological type of lung cancer in comparison to the control group

TNM CLASSIFICATION	Xmin	Xmax	Mean X	95% CI	Standard deviation (+/-)	Median	Significance
Non small cell carcinomastage IIA	101	150	130	117-142	19.3	137	p > 0.05
Non small cell carcinomastage IIB	95	146	124	116-131	16.3	125	
Non small cell carcinoma stage IIIA	85	179	122	118-126	16.9	121	
Non small cell carcinoma stage IIIB	94	162	128	122-134	16.5	129	
Non small cell carcinoma stage IV	86	160	121	116-125	18.3	119	

Legend: hemoglobin* = hemoglobin g/L; CI* = confidence interval

Table 2. Analysis of hemoglobin* levels between non small cell lung carcinoma subtypes

TNM CLASSIFICATION	Xmin	Xmax	Mean X	95% CI	Standard deviation (+/-)	Median	Significance
Small cell carcinoma (limited)	100	142	123	115-130	14.8	126	p > 0.05
Small cell carcinoma (extended)	94	158	128	120-135	18.2	128	

Legend: hemoglobin* = hemoglobin g/L; CI* = confidence interval

Table 3. Analysis of hemoglobin* levels between limited and extended stage of smal cell lung carcinoma

TNM CLASSIFICATION	Xmin	Xmax	Mean X	95% CI	Standard deviation (+/-)	Median	Significance
Non small cell carcinoma stage IIA, IIB	95	150	125	118-130	17.8	127	p > 0.05
Non small cell carcinoma stage IIIA, IIIB and IV	85	179	123	120-125	17.4	121	

Legend: hemoglobin* = hemoglobin values g/L; CI* = confidence interval

Table 4. Anallysis of hemoglobin* levels between earlier and advanced stage of non small cell carcinoma

PATIENTS	Xmin	Xmax	Mean X	95% CI	Stdandard deviation (+/-)	Median	Significance
Non small cell carcinoma	85	179	123	121-125	17.7	121	p > 0.05
Small cell carcinoma	94	158	126	121-131	15.7	130	

Legend: hemoglobin* = hemoglobin g/L; CI* = confidence interval

Table 5. Analysis of hemoglobin* levels between non small cell carcinoma and small cell carcinoma

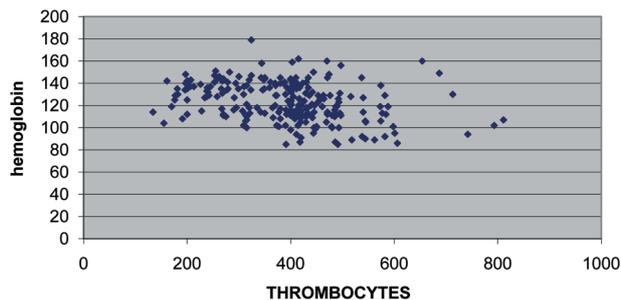


Figure 1. Correlation between platelet count and hemoglobin levels in patients with lung cancer

DISCUSSION

Low hemoglobin is commonly observed in lung cancer (2, 8, 9). Reactive thrombocytosis and simultaneously decreased hemoglobin values many authors found in lung carcinoma before treatment (5, 8, 10). The results reached by the authors cited above are similar to the results of our research.

The values of hemoglobin at diagnosis of lung cancer is considered as one of prognostic factors in survival of lung cancer patients. Many authors have found that low hemoglobin is negative prognostic factor in many malignancies, e. g. carcinoma of the urinary bladder (11), head and neck cancers (12), ovarian cancer (13) and cervix uteri cancer (14). Ikeda et al. examined the platelet count and hemoglobin levels as prognostic factors of survival in 369 patients with gastric cancer. Low hemoglobin values and thrombocytosis was significantly present in patients in advanced, inoperative stage of the disease. The authors found a positive correlation between the depth of tumor invasion, thrombocytosis, low hemoglobin values and a shorter survival time.

A number of authors have noted the diagnostic and prognostic importance of present thrombocytosis in patients with lung cancer (2–5). In their research they found that thrombocytosis indicates a rapid progression of cancer and shorter survival time. The authors (1–5, 8–10) believe that thrombocytosis indicates more malignant character of clinically suspected lung cancer than the traditional tumor markers.

Iron deficiency and anemia are often in patients with solid tumors. Iron deficiency and anemia contribute to the development of thrombocytosis, but the precise and exact mechanism of this interaction are unknown (15). Anemia is often present in patients with common in patients older than 65 years of age. Treatment of anemia and the maintenance of adequate hemoglobin concentration, among other things, prevents the formation of energy imbalances and emotional distress (16).

In our study, hemoglobin levels were significantly lower for each histological type of lung cancer, except for large cell carcinoma, compared to the control group. Analysis of hemoglobin levels in NSCLC compared to SCLC, showed no significant differences between histological types of cancer, nor between the individual stages as SCLC and NSCLC classified according to the TNM classification. In the available literature, we have not found an explanation for this phenomenon.

Anemia in patients with lung cancer can be caused by bleeding or paraneoplastic mechanisms. None of our patients had bleeding. Paraneoplastic mechanisms of anemia in patients with lung cancer have not been completely elucidated. It is assumed that cancer cells produce or induce the formation of cytokines such as interleukin, interferon or tumor factor, induce hemolysis, suppress or inhibit erythropoiesis induced by erythropoietin (17). It has been proven that the lack of erythropoietin stimulates platelet development in mice (18). However, the application of recombinant erythropoietin does not act significantly on the platelet count in adults (19).

Zeimet et al. found in their studies that the hemoglobin values were negatively correlated with thrombocytosis (20). Their results indicate that the association of low hemoglobin and thrombocytosis results in a shorter survival time of epithelial ovarian cancer patients. Kappen et al. have similar results (21). They have found that patients in advanced stages of cancer (stage III and stage IV), with present thrombocytosis, also have low hemoglobin and a shorter survival time.

In early stages of cancer (stage I and stage II), thrombocytosis was present in patients in a small percentage, almost proportional to the percentage of lower hemoglobin values. All cited authors believe that low hemoglobin and thrombocytosis are negative predictors of survival in patients with cancer.

Moyer P. examined how hemoglobin affects the survival time of patients with NSCLC (22). Patients with hemoglobin which was at least 12 g/dL. had significantly better survival time compared to those patients whose hemoglobin amounted to 10.5 g/dL, and even shorter survival time if the hemoglobin values were lower.

Unlike, thrombocytosis and low hemoglobin, in patients with gastric and gynecological cancers, are not an independent predictors of survival, because these cancers are associated with bleeding (1, 14).

More than half (81.1%) of our patients with lung cancer and thrombocytosis had decreased levels of hemoglobin. In patients with normal hemoglobin thrombocytosis was present in only 6.0% of patients with lung cancer. We also found a strong negative correlation

tion ($r = -0.87$) between hemoglobin levels and platelet count.

CONCLUSION

Hemoglobin levels in each histological type of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma) except for large cell carcinoma was significantly lower compared to the control

group. No significant difference in hemoglobin levels between different stages of lung carcinoma was found. Low hemoglobin levels were associated with thrombocytosis.

Based on the results of our study, we concluded that low hemoglobin in patients with lung cancer, with no evident hemoptysis, may have the character of paraneoplastic syndrome.

Sažetak

VRIJEDNOSTI HEMOGLOBINA KAO KOMPONENTA PARANEOPLASTIČNOG SINDROMA KOD KARCINOMA PLUĆA

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U zadnje vrijeme, neke studije ukazuju da paraneoplastični sindrom može biti prvi znak karcinoma pluća i može poslužiti u ranoj detekciji karcinoma. Zadnjih deset godina sve veći značaj pridaje se hematološkim parametrima kao pokazateljima paraneoplastičnog sindroma kod osoba oboljelih od karcinoma pluća. To su, prije svega, trombocitoza i niske vrijednosti hemoglobina.

Cilj ove studije bio je ispitati da li vrijednosti hemoglobina kod oboljelih od karcinoma pluća, određivane prije početka bilo koje vrste terapije, mogu pripadati paraneoplastičnom sindromu i ispitati korelaciju između vrijednosti hemoglobina i broja trombocita kod istih pacijenata.

Ova studija je obuhvatila 239 pacijenata sa karcinomom pluća koji su bili hospitalizirani na Klinici za plućne bolesti, Kliničkog centra Univerziteta u Sarajevu, u periodu od januara 2005. do decembra 2008. godine. U ovu studiju nisu bili uključeni pacijenti sa karcinomom pluća koji su imali evidentnu hemoptiziju, niti oboljeli od karcinomom pluća koji su primali hemoterapiju i/ili bili podvrgnuti hirurškom liječenju.

Kontrolna grupa od 60 ispitanika bile su zdrave osobe.

Srednje vrijednosti hemoglobina u našim istraživanjima statistički signifikantno su bile niže u odnosu na srednje vrijednosti hemoglobina kontrolne skupine, izuzev kod makrocelularnog karcinoma pluća. Statističkom obradom dobivenih vrijednosti hemoglobina kod bolesnika u različitim stadijima karcinoma pluća, klasificiranih prema TNM klasifikaciji, nismo našli značajnu razliku između pojedinih stadija razvoja karcinoma, kako nemikrocelularnog, tako ni mikrocelularnog karcinoma pluća.

Rezultati našeg istraživanja testirani testom korelacije, pokazali su negativnu korelaciju između broja trombocita i vrijednosti hemoglobina.

Na osnovu naših istraživanja zaključili smo da niske vrijednosti hemoglobina kod pacijenata sa karcinomom pluća, bez evidentne hemoptizije, mogu imati karakter paraneoplastičnog sindroma.

Ključne riječi: vrijednosti hemoglobina, karcinom pluća, trombocitoza.

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