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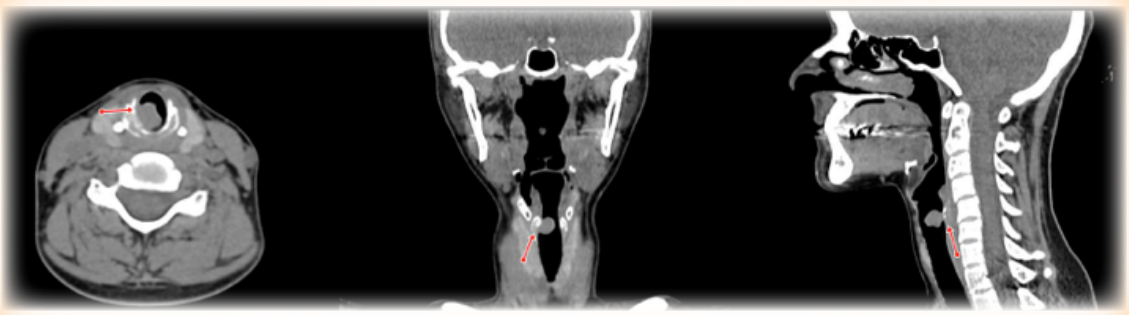
CURRENT THORACIC SURGERY



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Original Articles

Case Report

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Original Article

The prognostic significance of the systemic immune-inflammatory index in surgically treated non-small cell lung cancers

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ABSTRACT

Background: Lung cancer is a leading cause of cancer-related deaths worldwide, and the majority of lung cancer deaths are due to non-small cell cancers. The most important indicator of prognosis in lung cancer is the tumor stage. In recent years, studies investigating the correlation between cancer development, prognosis, and inflammation have increased. In our study, the prognostic efficacy of the systemic immune-inflammation index (SSI) was investigated in patients with surgically treated non-small cell lung cancer in pathologic stage III-A, according to the eighth edition TNM stage classification.

Materials and Methods: Following the approval of the local ethics committee, the data of patients with stage III-A lung cancer who were operated on in our clinic between January 2010 and December 2019 were retrospectively analyzed. In accordance with the definitions in the literature, systemic immune-inflammation index groups were calculated using the following formula: (neutrophil count) x (platelet count) / (lymphocyte count) in the preoperative complete blood count tests of patients; the cut-off value was determined by ROC analysis. According to this value, high and low SSI groups were created. The survival difference between the groups was determined by Kaplan–Meier, log-rank, and Cox regression analysis.

Results: A total of 181 patients were included in the study -27 women and 154 men. The median age was 62 (age range: 25 - 82), and the median tumor diameter was 4.5 cm (0.1 - 10 cm). The cut-off value for the SII was calculated as 1,046.105 by ROC analysis. There were 27 patients in the high SSI group and 154 patients in low SSI group. Survival was significantly worse in the high SSI group (P = 0.02, HR: 1.9, 95% CI). In addition, survival was significantly worse in the pneumonectomy group (P = 0.01).

Conclusions: Using the SSI is a simple and inexpensive way to predict prognosis in patients with stage III-A lung cancer who are treated surgically.

Keywords: lung cancer, prognosis, systemic immune-inflammatory index

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Although the most important prognostic factor of lung cancer is tumor stage, attempts have been made to determine additional prognostic markers. In the literature, some studies investigating the relationship between inflammation, cancer development, and prognosis of malignancy in various cancer types have been published [2-4]. The systemic immune-inflammation index (SII) is calculated with values obtained from a complete blood count (CBC) test, and it used in prognosis prediction in various cancers. The SII calculation formula is as follows: (platelet count) x (neutrophil count) / (lymphocyte count) [5].

The aim of our study is to determine whether there is a correlation between SII and prognosis in surgically treated stage III-A (according to the eighth edition TNM stage classification) non-small cell lung cancers (NSCLC).

Materials and Methods

Patient selection

According to approval of the local ethic committee (2020-37), the data of the patients who were operated with the diagnosis of non-small cell lung cancer (NSCLC) in our clinic between January 2010 and December 2019 were retrospectively analyzed. Those with stage III-A (T1N2M0, T2N2M0, T3N1M0, T4N1M0, T4N0M0) according to the eighth TNM staging of pathological staging were included the study. The following patients were not included the study; patients who received neo-adjuvant therapy, who had active infection, who could not receive adjuvant therapy and patients whose follow-up records could not be obtained. The SII values of patients were calculated as (platelet count) x (neutrophil count) / (lymphocyte count) in accordance with previous study in the literature. For this, preoperative CBC tests were used. The cut-off value for SII was calculated by Receiver Operator Characteristics (ROC) analysis and high and low SII groups were created based on this value. The data of patients were analyzed according to age, gender, lymph node metastasis, surgery performed and SII cut-off values.

Statistical Analysis

All analyses were performed with the SPPS program, version 20 (IBM, USA). Overall survival (OS) was defined as the date from surgery to the date of death or, for living patients, the date of study. Overall survival analysis was performed using the Kaplan–Meier method, and the significance of the difference in survival between groups was investigated using the log-rank and Cox regression test methods. All analyses were performed in 95% confidence intervals (CI), two-sided P values were calculated, and $P < 0.05$ value was considered statistically significant.

Results

Descriptive analyses

A total of 181 patients who fulfilled the inclusion criteria were included in the study. The demographic and clinical-pathologic features of patients are provided in Table 1.

Twenty-seven patients (14.9%) were female, and 154 patients (85.1%) were male. The median age was 62 (age range: 35 - 82), and the median tumor diameter was 4.5 cm (0.9 - 10 cm). In histopathological examinations, N2 station lymph node metastasis was detected in 94 patients (51.9%), and N1 was detected in 41 patients (22.7%). The cut-off value of SII in our series was calculated as 1,046 x 105 by ROC analysis (Figure 1). When groups were formed according to this value, 27 patients were in the high SII group and 154 patients in the low SII group. The largest subgroup of stage III-A of our series according to the eighth edition TNM stage classification was T1N2M0, which included 61 patients (33.7%). Visceral pleural invasion was detected in 77 patients (42.6%) and parietal pleural invasion in nine patients (4.9%).

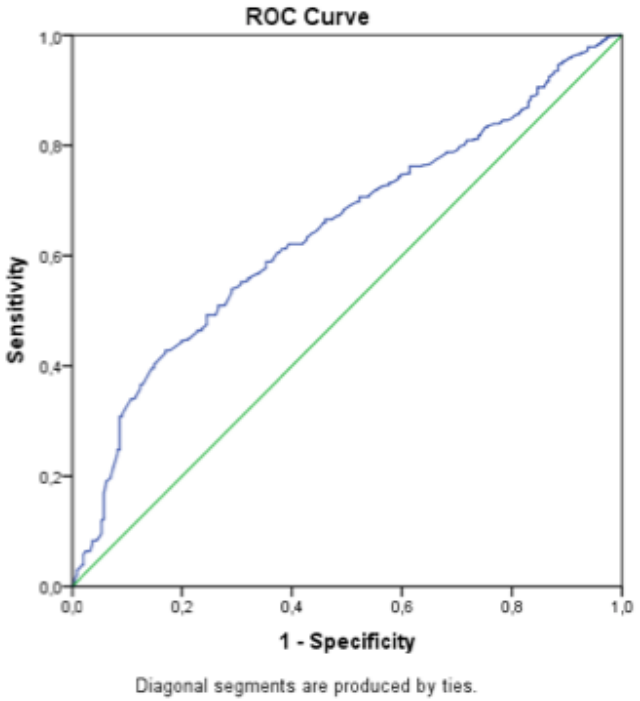

Figure 1. ROC (Receiver Operator Characteristics) curve of our study for SII.

Table 1. The clinico-pathologic/demographic features and p values of patients, n=181.

Variables		n	%	Median Survival (months)	p
Age (med)	62 (Range:25-82)				
Tumor diameter (med)	4.5 cm (Range: 0.1-10 cm)				
Gender					
	Female	27	14.9	35	0.7
	Male	154	85.1	37	
Age					
	>65	41	22.6	35	0.4
	≤65	140	77.4	43	
Stage subgroups (8thTNM)					
	T1N2M0	61	33.7	52	
	T2N2M0	33	18.2	33	
	T3N1M0	26	14.4	37	0.041
	T4N1M0	16	8.8	35	
	T4N0M0	45	24.9	37	
SII Value2					
	> cut-off	27	14.9	31	0.02
	< cut-off	154	85.1	43	
Type of Surgery	Lobectomy + MLND	101	55.8	51	
	Segmentectomy + MLND	3	1.7	33	
	Pnemonectomy + MLND	43	23.8	20	0.013
	Sleeve lobectomy + MLND	9	5	36	
	Lung resection with CWR + MLND	10	5.5	34	
	Bilobectomy + MLND	15	8.3	44	
VPI					
	Yes	77	42.6	35	
	No	95	52.5	52	0.6
	PPI	9	4.9	37	

Explanations: 1. The median survival of T2N2M0 subgroups was significantly worse than others, 2. The cut-off value of our series was calculated as 1,046.105 , 3. Survival difference between lobectomy and pneumonectomy groups was statistically significant.

Abbrev.: CWR: Chest wall resections, Med: median, MLND: Mediastinal lymph node dissection, PPI: Parietal pleural invasion, SII: Systemic immune-inflammatory index, TNM: Tumor-Node-Metastasis staging system, VPI: Visceral pleural invasion.

Survival analysis

The median survival in our study was 37 months (26.4 - 47.5), and the five-year OS was 35.5% (Figure 2). There was no correlation between gender and survival. The median survival was 31 months in the high SII group and 43 months in the low SII group, and the difference was statistically significant (P = 0.02, HR:1.9, 1.1-3.4, 95% CI) (Figure 3). There was no statistically significant difference between survival and pleural invasion status and age. Survival was significantly worse in the pneumonectomy group and in the T2N2M0 subgroup (P = 0.001 and 0.04, respectively).

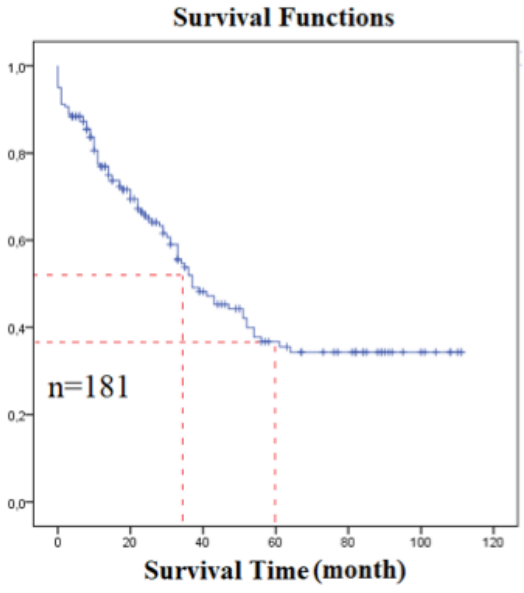

Figure 2. Overall survival curve (Kaplan-Meier).

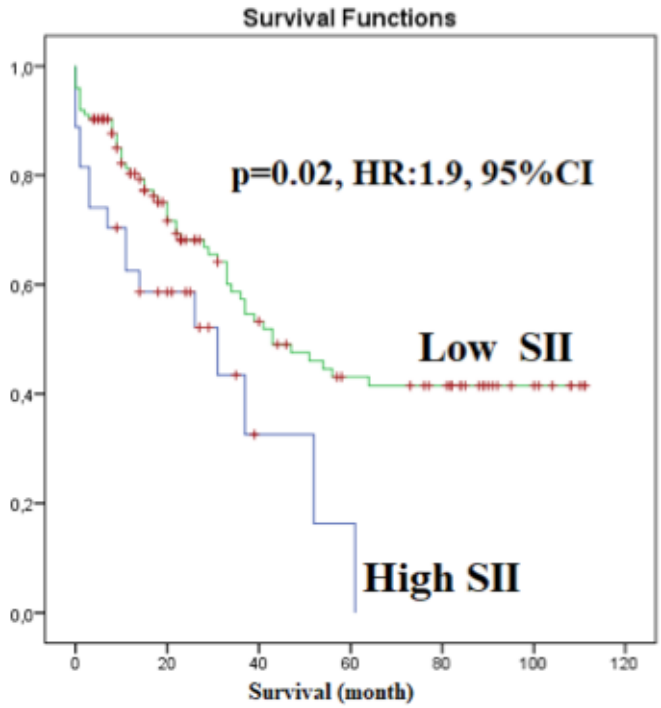

Figure 3. When survival comparison was made in high and low SII groups, it was seen that the survival was significantly worse in high SII group.

Discussion

Lung cancer is one of the leading causes of cancer-related deaths worldwide; nearly 80% of lung cancer deaths are due to NSCLC [6]. Recently, serum inflammatory parameters have been emphasized in studies as a way to determine the prognosis of variable cancers. In the literature, studies have indicated a correlation between high platelet-lymphocyte ratio (PLR) and high neutrophil-lymphocyte ratio (NLR) and poor prognosis. Some studies have reported that neutrophils were increased by the cytokine effect in malignant tumors and play an important role in tumorigenesis and angiogenesis [7-9]. Other studies have shown that tumor cells were protected from the phagocytic effect of macrophages by complexing with the platelet; therefore, the serum platelet count indicated tumor aggressiveness [10,11]. Within regard to the number of lymphocytes, the situation reverses because lymphocytes have an antitumor effect. Some studies have shown that a high lymphocyte count is associated with good survival in patients with a malignant tumor [12,13].

The SII is a combination of these parameters and is calculated by platelet, neutrophil, and lymphocyte counts in preoperative CBC tests of patients. Gao et al reported that the SII was a strong indicator of prognosis in their studies investigating the correlation between operable non-small cell lung cancers and the SII [14]. Hong et al. showed a significant correlation between the SII, serum LDH level, tumor stage, and survival in small cell lung cancers [15]. Guo et al found that the SII was a superior indicator in terms of prognosis compared to NLR and PLR in surgically resected lung cancer, especially in the adenocarcinoma subgroup [16]. Another study investigating survival in advanced stage lung cancers reported that disease- free survival (DFS) and OS were significantly worse in the high SII group than in the low SII group [5]. Deng et al found worse outcomes in terms of DFS and OS in the high SII group in patients with advanced lung adenocarcinoma treated with tyrosine kinase inhibitors [17]. In a meta-analysis related to the subject, it was concluded that the SII is a poor prognostic factor for lung cancer [18]. In our study, we aimed to provide prognosis homogeneity by selecting cancer patients at the same disease stage. In accordance with the literature, we determined the SII cut-off value for our patient series by ROC analysis, and we formed a high and a low SII group. In the high SII group, median survival and five-year OS were significantly worse. Other significant factors in poor prognosis in our study were pneumonectomy and the T2N2M0 subgroup.

The limitations of our study are that it was single-centered and retrospective and the number of patients included was relatively low.

In conclusion, the SII can be used as a simple, inexpensive, and easily applied marker in the prediction of prognosis of patients with stage III-A lung cancer who are treated surgically. However, this result needs to be supported by prospective, randomized, and multicenter studies.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Original Article

Changes in neutrophil to lymphocyte ratio after non-small cell lung cancer resection: a retrospective cohort study

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ABSTRACT

Background: Increasing neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) define and grade systemic inflammation in lung cancer patients. We hypothesized a decrease in NLR and PLR after tumor resection, and their potential prognostic value in follow-up.

Materials and Methods: Adult patients diagnosed previously (and/or histopathologically after lung surgery) with NSCLC were enrolled from the1st January 2016 to 1st January 2018. Patients were grouped according to tumor size (≥ 5 cm and < 5 cm) and sub-grouped by gender and type of surgery (lobectomy and pneumonectomy). Patient information was recorded from the hospital database and included age, gender, hemogram and blood biochemistry values, results, and before and after lung resection. Total leukocyte count, neutrophil count, NLR, PLR, PLT/MPV, and C-reactive protein (CRP) were recorded and calculated. Mortality was recorded during the follow-up period.

Results: Among the 314 included patients (56, 18% female, mean age 60 years, SD=11) pneumonectomy and lobectomy numbers were 56 (18%) and 258 (82%), respectively, and 92 (29%) patients had larger tumors and 222 (71%) had smaller tumors NLR, PLR and CRP median values immediately before and after tumor resection were 17.08 vs. 10.03, P < 0.001, 315.61 vs. 215.10, P < 0.001, and 9.0 vs. 9.5, P = 0.10, respectively. Median follow-up was 300 days (IQR 198-381), and 36 (11.5%) patients died. Cox regression showed that a post-operative NLR ≥ 12.0 was a significant prognostic indicator (HR: 2.09, CI 95% [1.08-4.06], and P = 0.029).

Conclusions: NLR >12 after lung resection may be an important prognostic value for six-month mortality. NLR and PLR may be useful biomarkers in NSCLC immediately post-surgery and for long-term follow-up.

Keywords: lung cancer, neutrophil, lymphocyte, biomarkers, thoracic surgery

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Introduction

Lung cancer is the second highest cause of worldwide deaths, inclusive of both high and low-income countries, and non–small cell cancer (NSCLC) is observed in approximately 85% of lung cancers [1]. Surgery is the standard treatment of stage 1 and stage 3A lung cancers [2]. Tumor cell spreading is established by angiogenesis and cancer cell proliferation [3,4] and the T and B lymphocytes and neutrophils are indicated to have a role in tumor inflammation (spreading). An increasing neutrophil to lymphocyte ratio (NLR) is reported to define, as well indicate the degree, of systemic inflammation in patients with tumors [5,6].

Recent studies have shown promising results in defining novel inflammatory biomarkers in lung cancer that may indicate the progression of disease or response to therapy. These studies show that an increased preoperative or pre-treatment NLR and platelet to lymphocyte ratio (PLR) (calculated from peripheral blood tests) have been found to be independent and easy, low cost prognostic biomarkers in patients with lung cancer, including small cell and non-small cell lung cancer [7-10]. There have been limited studies in patients with NSCLC who have undergone a lung resection and where NLR and PLR are evaluated as survival predictor biomarkers [11,12]. NLR and PLR indices are not well studied in terms of acute changes immediately after lung resection with different size tumors in patients with NSCLC.

In the present study, we hypothesized that NLR is an index of systemic inflammation in patients with NSCLC where the larger tumors (≥ 5 cm) may result in higher NLR and PLR ratios, and these biomarkers may decrease immediately after tumor resection. We also aimed to determine six-month survival rates after lung resection and to assess whether a decrease in NLR and PLR were indicative of a more promising survival rate.

Materials and Methods

This study was a retrospective, cohort designed study conducted in Health of Science University Sureyyapasa Chest Diseases and Thoracic Surgery Teaching and Research Hospital. The study was approved by the local ethical committee of the hospital (14.05.2018/036) and was conducted in accordance with the principles of the Declaration of Helsinki. All study data were collected retrospectively from the hospital electronic database. Due to the retrospective nature of the study, informed consent was not obtained from the patients for the use of medical data for publication purpose, and this was waived by the institution's local scientific committee, in line with the local legislation. All patients' ID information was strictly protected. This study has been reported in line with the STROCSS criteria [13].

Patients

Adult patients (aged 18 and above) were enrolled in the study, if diagnosed with NSCLC previously and/or histopathologically after lung surgery in the study period (1st January 2016 to 1st January 2018). Adenocarcinoma, epidermoid carcinoma and lung cancer other than small cell lung cancer were also defined. Patient enrollment, inclusion criteria and exclusion criteria are summarized in Figure 1. Patients were grouped according to tumor size, i.e., larger tumor (≥5 cm) and smaller tumor (<5 cm) and sub-grouped by gender and type of surgery (lobectomy and pneumonectomy).

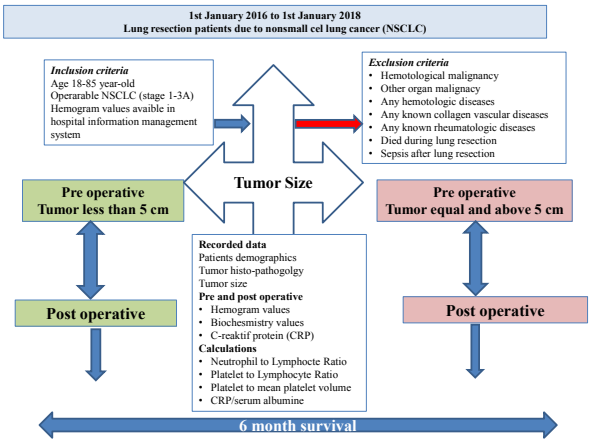

Figure 1. Flow chart.

Definitions and Calculations

Neutrophil lymphocyte ratio (NLR): As a marker of systemic inflammation NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Elevated NLR values were accepted as five or above, as defined previously [15]. NLR was further grouped as dichotomous at five and according to cutoff values for long-term mortality.

Platelet to lymphocyte ratio (PLR): PLR was defined as the absolute platelet count divided by absolute lymphocyte count. A PLR of 300 was defined as elevated, and was grouped as dichotomous above and below 300 [15].

Platelets/MPV ratio: As a marker of systemic inflammation the ratio of platelet count to mean platelet volume was calculated.

C- reactive protein/serum albumin ratio (CAR): Defined as the ratio of CRP to serum albumin as a prognostic value of pretreatment in solid tumors [16].

Delta values of NLR; PLR; PLT/PMV; CAR; CRP: Defined as pre-operative values minus post-operative values.

Recorded Data

Patient information recorded from the hospital database included age, gender, hemogram and blood biochemistry values, and laboratory results on admission to the hospital, before and after lung resection. The type of histopathology's reported by the pathology specialists were adeno cancer, epidermoid cancer, large cell cancer and others. As inflammatory markers, total leukocyte count, neutrophil count, NLR, PLR, PLT/MPV, C-reactive protein (CRP), and CRP/serum albumin were recorded and calculated.

Whole blood cell counts including total leukocyte, neutrophil, eosinophil, lymphocyte, platelet counts, and MPV were determined using a Coulter LH 780 Hematology Analyzer (Beckman Coulter, USA). CRP was determined using the nephelometry method BN II System (Siemens, Germany). The normal range of CRP is 0-5 mg/L.

Statistical Analysis

Statistical analyses were done using the portable SPSS-20 version package program. Patient demographics and all clinical data were summarized by descriptive analysis. The Student's t-test was used for continuous variables, e.g., age, hemogram values, biochemistry values, NLR, PLR, PLT/MPV, and CRP, if distributed normally between the two groups. The values from the Student's t-test were shown as the median ± standard deviation (SD). If the groups were distributed non-normally, the non-parametric Mann-Whitney U test was used, and the values were shown as the median and inter quartile range (IQR, 25% and 75%). Dichotomous values (i.e. gender, types of tumor pathology, and tumor size) were compared using the Chi-Square test. For non-parametric values, the Wilcoxon Signed Rank test was used to compare pre- and post-operative hemogram and biochemistry values and biomarkers. The Spearman's rho, non-parametric correlations test was used for group correlations with inflammatory biomarkers. To define the long-term mortality cut-off values of NLR, PLR, PLT/MPV, and CPR, the receiver operating characteristic (ROC) curve was used, and the area under the curve (AUC) was obtained to determine the optimal cut-off values. Kaplan Meier survival analysis was used for long-term survival for researched inflammatory biomarkers. The Cox Regression hazard analysis was performed for patients who underwent lung resection due to non-small cell lung cancer. NLR values pre-and post-surgery greater than 5and 12, respectively, and PLR values above 300 were included in the model [12]. A p-value less than 0.05 was accepted as statistically significant.

Results

In the study period 314 eligible (56[18%] female) patients were enrolled. The mean age was 60 years (SD 11 years). The median tumor size was 3.5 cm (IQR 2.5-5.0 cm). The pneumonectomy and lobectomy numbers were 56 (18%) and 258 (82%), respectively. Patients were grouped according to tumor size as ≥ 5 cm (n = 92, 29%) and < 5 cm (n = 222, 71%). The types of NSCLC were as follows; 105 (33%) had adeno cancer, 158 (50%) had epidermoid cancer, 4 (1.3%) had large cell cancer, and 47 (15%) had other types.

Table 1 summarizes the pre- and post-operative hemogram and biochemistry values of the 314 patients with NSCLC. Clinically important and statistically significant changes were observed in blood glucose and serum albumin levels.

Table 2 shows a comparison of biomarkers between patient's grouped according to tumor size (≥ or < 5 cm). The group with the larger tumor size (≥ 5 cm) were older and all the biomarkers assessed had significantly unfavorable values, except for WBC and NLR. There were no significant differences in biomarkers before and after surgery in both tumor size groups.

Table 1. Patient hemogram and biochemistry values pre and post non-small cell lung cancer surgery.

	Pre-operative				Post-operative				
	N	Median	25%	75%	Valid n	Median	25%	75%	P*
Hemogram values									
WBC (109/L)	314	14.0	10.8	17.5	314	13.6	11.0	16.5	0.001
Neutrophil (109/L)	314	12.4	9.0	15.6	314	11.4	9.0	14.4	<0.001
Lymphocyte (109/L)	313	0.8	0.5	1.2	314	1.1	0.8	1.5	<0.001
Monocyte (%)	314	5.1	3.7	6.8	314	5.8	4.3	7.0	<0.001
Eosinophil (%)	314	0.1	0.0	0.5	314	0.1	0.0	0.3	0.35
Basophil (%)	314	0.3	0.1	0.6	314	0.2	0.1	0.5	0.051
RBC (1012/L)	314	4.32	3.97	4.68	314	4.17	3.76	4.53	<0.001
Hemoglobin (g/dL)	313	12.5	11.1	13.4	314	11.8	10.7	13.0	<0.001
Hematocrit (%)	313	37.7	33.6	40.7	314	36.0	32.5	39.1	<0.001
RDW-CV (%)	313	14.7	13.7	15.7	314	14.8	13.9	15.9	<0.001
PLT(109/L)	314	250	199	303	314	242	193	293	0.031
MPV (fL)	314	8.4	7.6	9.2	314	8.6	7.9	9.3	<0.001
PCT (%)	314	0.21	0.17	0.25	314	0.21	0.17	0.25	0.49
Biochemistry									
Glucose (mg/dL)	314	105	95	136	314	122	99	145	0.001
BUN (mg/dL)	313	31	25	39	314	31	25	40	0.28
Creatinine (mg/dL)	313	0.79	0.66	0.91	314	0.78	0.64	0.90	0.21
Albumin (g/dL)	301	4.1	3.6	4.3	313	3.4	3.1	3.9	<0.001
Sodium (mmol/L)	309	140	138	141	314	139	136	141	<0.001
Potassium (mmol/L)	312	4.3	4.2	4.6	313	4.3	4.1	4.6	<0.001
Calcium (mg/dL)	309	9.0	8.8	9.4	312	8.8	8.3	9.1	<0.001
SGOT (U/L)	312	23	18	26	314	28	23	40	<0.001
SGPT (U/L)	311	19	14	25	312	20	15	25	0.44

*Wilcoxon signed rank test.
Abbrev. : WBC: white blood cell; RBC: red blood cell; PLT: platelet; RDW-CV: red cell distribution width; MPV: mean platelet volume; PCT: plateletcrit; BUN: blood urea nitrogen; SGOT: serum glutamate oxaloacetate transaminase; SGPT: serum glutamate pyruvate transaminase.

The biomarkers were similar for both males and females pre- and post-lung resection except for post-operative NLR, which was significantly greater in males compared with females (Table 3).

Table 4 shows pre-operative and post-operative biomarkers in all patients' subgrouped according to the type of lung resection and tumor histopathology. Apart from CRP, all the biomarkers assessed showed statistically significant changes.

Figures 2a and b show changes in the NLR, PLT/MPV, CRP and PLR median values from the pre- to post-operative period. After tumor resection NLR, PLR were favorably decreased, while CRP was unchanged. The PLT/MPV changes were not clinically relevant.

Table 5 summarizes the comparison of biomarkers of patients who underwent pneumonectomy and lobectomy. Pre-postoperative PLR were significantly unfavorably higher in patients with pneumonectomy. All other biomarkers were similar for both types of surgery.

Table 6 shows a correlation of the studied biomarkers with tumor size and each other. Pre-operative PLR and PLT/MPV showed significance correlation with tumor size. Delta changes (defined as the pre-operative value minus the post-operative value), showed that delta NLR correlated well with delta PLR and delta WBC but not delta CRP. Delta PLR correlated weakly with delta WBC, and delta PLT/MPV, but not delta CRP.

Table 2. A comparison of inflammatory biomarkers according to tumor size in lung cancer patients who underwent resection.

	Tumor Size <5 cm				Tumor Size ≥5 cm				P*
	N	Median	25%	75%	N	Median	25%	75%	
Age, year	222	61	53	65	92	64	58	69	0.001
Tumor size, cm	222	3.0	2.0	3.6	92	6.0	5.4	7.5	<0.001
Pre-op NLR	222	16.96	9.33	25.67	92	18.93	9.52	26.55	0.89
Post-op NLR	222	10.1	6.67	16.09	92	11.25	8.55	16.4	0.18
Pre-op PLR	222	289.33	182.14	434	92	364.57	229.17	491.67	0.030
Post-op PLR	222	194.64	150	280	92	264.83	188.55	334.24	<0.001
Pre-op PLT/MPV	222	29.39	20.78	37.03	92	31.31	25.2	43.13	0.005
Post-op PLT/MPV	222	27.21	19.17	35	92	31.66	25.24	39.39	0.001
Pre-op CRP mg/dL	85	7.8	3.5	23	43	20.5	4.5	66.1	0.030
Post-op CRP mg/dL	91	6.3	3.2	19.5	44	27.7	6.2	131.5	0.003
Pre-op WBC	222	13.9	10.3	17.5	92	14.2	11.4	17.3	0.62
Post-op WBC	222	13.7	10.8	16.4	92	13.5	11.2	16.7	0.93
Pre-op CAR	84	1.92	0.95	5.6	43	5.76	1.16	18.89	0.027
Post-op CAR	90	1.66	0.94	5.92	44	7.61	1.89	42.34	0.001
Delta NLR	222	7.04	0.29	12.57	92	6.35	0.11	13.23	0.66
Delta PLR	222	83	-9.31	198.17	92	92.99	-20.87	232.91	0.82
Delta PLT/MPV	222	1.35	-0.72	3.73	92	0.52	-2.71	4.21	0.24
Delta CRP	83	1.09	-2.87	11.6	42	0.94	-23.64	30.3	0.85
Delta CAR	80	0.29	-0.76	2.40	42	0.00	-6.38	6.77	0.52

*Mann Whitney-U test.

Abbrev. :Pre-op: pre-operative; Post-op: post-operative; Delta: pre-operative value minus post-operative value; WBC: white blood cell; CRP: C reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet ratio; CAR: C reactive protein to serum albumin ratio.

Table 3. Inflammatory biomarkers according to gender in patients who had undergone lung cancer resection.

	Gender								
	Female, n=56				Male, n=258				
	N	Median	25%	75%	N	Median	25%	75%	P*
Pre-op NLR	56	17.38	7.52	23.70	258	17.08	9.44	26.67	0.45
Post-op NLR	56	8.75	6.28	13.31	258	11.06	7.43	16.50	0.020
Pre-op PLR	56	321.55	181.33	459.44	258	315.61	198.00	452.00	0.82
Post-op PLR	56	190.25	146.70	283.75	258	218.14	162.50	311.43	0.21
Pre-op PLT/MPV	56	31.68	24.43	39.01	258	29.46	21.65	38.59	0.22
Post-op PLT/MPV	56	28.96	22.60	37.80	258	28.23	20.76	35.00	0.30
Pre-op CRP	19	6.3	3.4	12.4	109	12.6	3.7	43.0	0.12
Post-op CRP	20	4.6	3.2	16.3	115	10.8	3.5	76.4	0.08
Pre-op WBC	56	13.3	10.1	17.1	258	14.3	10.9	17.5	0.36
Post-op WBC	56	13.1	11.0	16.1	258	13.7	11.0	16.5	0.45

*Mann Whitney-U test.

Abbrev.: WBC: white blood cell; CRP: C reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet ratio.

Table 4. Inflammatory biomarkers pre- and post-lung resection in patients with lung cancer.

	Pre-operative				Post-operative				
	N	Median	25%	75%	N	Median	25%	75%	P*
Lobectomy									
WBC count x109	258	13.9	10.28	17.25	258	13.6	10.9	16.23	0.001
CRP, mg/dL	111	8.12	3.72	31.4	116	7.78	3.27	41.93	0.10
NLR	258	16.78	8.77	25.43	258	10.23	6.65	15.78	<0.001
PLR	258	298	176.67	429.55	258	200.45	152.08	293.14	<0.001
PLT/MPV	258	29.46	21.96	37.6	258	27.81	20.59	35.12	<0.001
Pneumonectomy									
WBC count x109	56	14.7	11.33	17.83	56	13.5	11.65	17.28	0.40
CRP, mg/dL	17	22	3.93	46.3	19	30.3	5.6	117	0.96
NLR	56	21.19	11.68	29	56	11.33	8.7	16.92	<0.001
PLR	56	374.2	242.38	506.07	56	264.21	181.91	362.92	<0.001
PLT/MPV	56	31.56	22.81	42.67	56	31.81	22.74	38.16	0.50
Adeno Cancer									
WBC count x109	105	13.4	9.9	18.0	105	13.5	11.1	16.6	0.020
CRP, mg/dL	48	7.3	3.5	22.5	50	10.2	3.5	48.2	0.98
NLR	105	15.43	7.92	24.71	105	10.92	7.19	15.75	<0.001
PLR	105	258.33	174.76	425.00	105	218.18	154.67	293.33	<0.001
PLT/MPV	105	27.79	21.98	36.84	105	26.91	18.95	33.37	<0.001
Epidermoid cancer									
WBC count x109	158	14.6	11.3	17.5	158	13.9	11.4	17.0	0.020
CRP, mg/dL	61	18.2	4.5	56.0	65	14.7	5.2	51.6	0.08
NLR	158	19.32	10.42	28.50	158	10.77	7.67	16.57	<0.001
PLR	158	332.05	230.00	490.00	158	223.89	165.45	331.82	<0.001
PLT/MPV	158	30.35	22.37	39.88	158	29.04	21.56	36.54	0.005

*Wilcoxon signed rank test.
Abbrev.: WBC: white blood cell; CRP: C reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet ratio.

Table 5. Inflammatory biomarkers in patients with lung cancer according to the type of lung resection.

	Pneumonectomy, n=56				Lobectomy, n=258				P*
	N	Median	25%	75%	N	Median	25%	75%	
Pre-op NLR	56	21.19	11.87	29.00	258	16.78	8.81	25.40	0.07
Post-op NLR	56	11.33	8.71	16.91	258	10.23	6.67	15.75	0.07
Pre-op PLR	56	374.20	245.75	502.14	258	298.00	177.22	428.57	0.008
Post-op PLR	56	264.21	183.15	356.94	258	200.45	152.78	293.08	0.016
Pre-op PLT/MPV	56	31.56	22.86	42.65	258	29.46	21.98	37.50	0.18
Post-op PLT/MPV	56	31.81	22.83	37.87	258	27.81	20.59	35.06	0.12
Pre-op CRP mg/dl	17	22.0	4.5	46.3	111	8.1	3.7	31.4	0.39
Post-op CRP	19	30.3	5.6	117.0	116	7.8	3.3	40.0	0.10
Pre-op WBC count	56	14.7	11.4	17.8	258	13.9	10.3	17.2	0.37
Post-op WBC count	56	13.5	11.7	17.3	258	13.6	10.9	16.2	0.33

* Wilcoxon signed rank test.
Abbrev.: WBC: white blood cell; CRP: C reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet ratio.

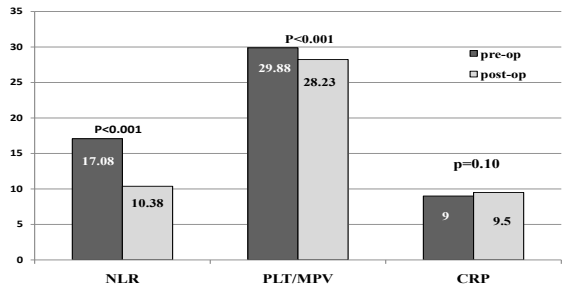

Figure 2a. NLR, PLT/MPV and CRP median values from the pre- to post-operative period. After tumor resection NLR were favorably decreased, while CRP was unchanged. The PLT/MPV changes were not clinically relevant.

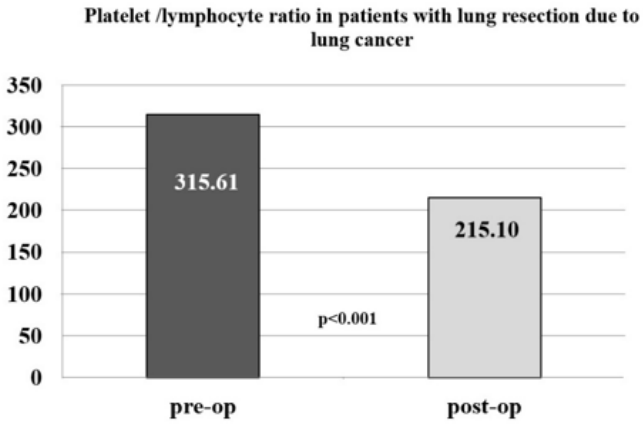

Figure 2b. PLR median values from the pre- to post-operative period. After tumor resection PLR were favorably decreased.

Table 6. A correlation of inflammatory biomarker changes with tumor size pre- and post-lung resection in patients with non-small cell lung cancer.

Values	r	P *
Tumor size and delta NLR	-0.02	0.67
Tumor size and pre-op NLR	-0.00	0.95
Tumor size and delta PLR	0.02	0.79
Tumor size and pre-op PLR	0.12	0.036
Tumor size and delta PLT/MPV	-0.05	0.39
Tumor size and pre-op PLT/MPV	0.23	<0.001
Tumor size and delta CRP	0.01	0.89
Tumor Size and pre-op CRP	0.19	0.030
Delta NLR and delta PLR	0.86	<0.001
Delta NLR and delta PLT/MPV	-0.01	0.88
Delta NLR and delta CRP	-0.23	0.010
Delta NLR and delta WBC count	0.42	<0.001
Delta PLR and delta PLT/MPV	0.18	0.001
Delta PLR and delta CRP	-0.16	0.08
Delta PLR and delta WBC	0.21	<0.001
Delta PLT/MPV and delta CRP	0.16	0.07
Delta PLT/MPV and delta WBC	0.18	0.001
Delta CRP and delta WBC count	-0.01	0.96

*Spearman's rho, non-parametric correlations.

Abbrev.: Pre-op: pre-operative; Post-op: post-operative; delta: pre-operative value minus post-operative value; WBC: white blood cell; CRP: C reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet ratio.

Figure 3 shows the cutoff values for mortality in the pre-operative period for NLR were 20.55 (sensitivity 61%, specificity 62%), and 12 in the post-operative period (sensitivity 58%, specificity 62%). In Figure 3 of the Area Under the Curve for biomarkers in 36 non-survivors with NSCLC were summarized in Table 7.

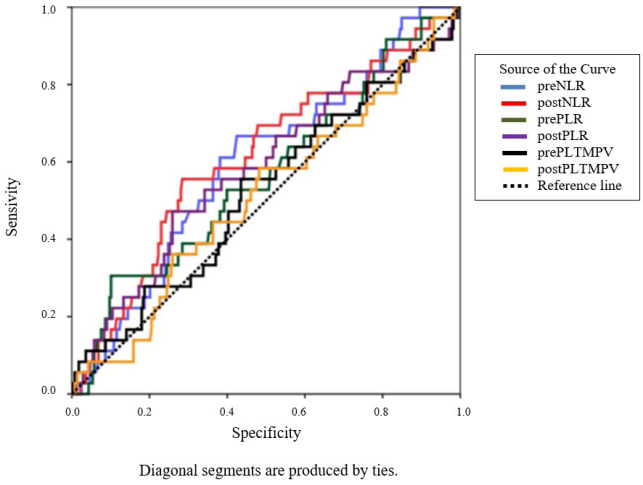

Figure 3. The ROC curve for mortality biomarkers in patients with NSCLC in long term follow-up.

Table 7. Area Under the Curve for biomarkers in 36 non-survivors with NSCLC.

Test Result Variable(s)	Area	P	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
Pre-operative NLR	0.60	0.07	0.50	0.69
Post-operative NLR	0.61	0.03	0.51	0.71
Pre-operative PLR	0.56	0.22	0.46	0.67
Post-operative PLR	0.58	0.12	0.48	0.69
Pre-operative PLT to MPV	0.52	0.67	0.42	0.63
Post-operative PLT to MPV	0.51	0.82	0.41	0.61

Abbrev.: Pre-op: pre-operative; Post-op: post-operative; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; MPV: mean platelet volume.

Figures 4a and b show the long-term survival of patients with NSCLC after surgery in a Kaplan Meier analysis of a post-operative NLR of 12.0 and tumor size 5 cm and greater.

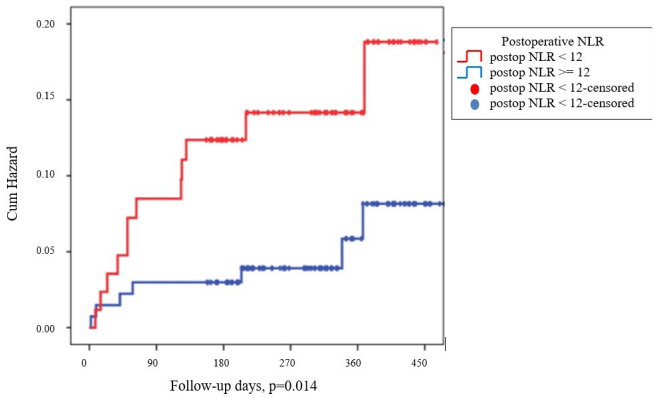

Figure 4a. Long-term survival of patients with NSCLC after surgery in a Kaplan Meier analysis of a post-operative NLR of 12.0 and tumor size less than 5 cm.

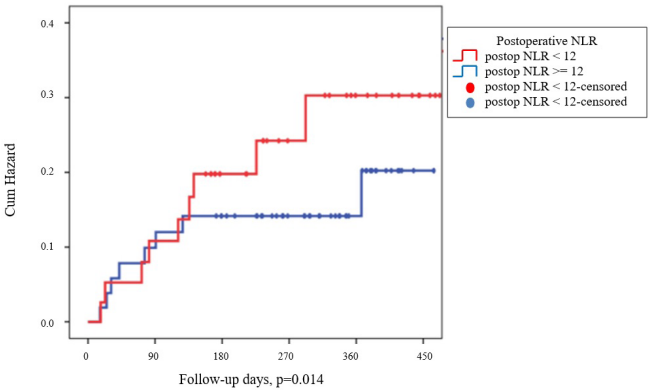

Figure 4b. Long-term survival of patients with NSCLC after surgery in a Kaplan Meier analysis of a post-operative NLR of 12.0 and tumor size 5 cm and above.

Figure 5 shows the Cox regression hazard ratio analysis of 36 non-survivors during the follow-up period. Pre- and post-surgery values of NLR > 5 and > 12, respectively and PLR values above 300 were included in the model. A post-operative NLR of 12.0 and above showed a significant hazard ratio (HR: 2.09, CI 95% [1.08-4.06] and P = 0.029).

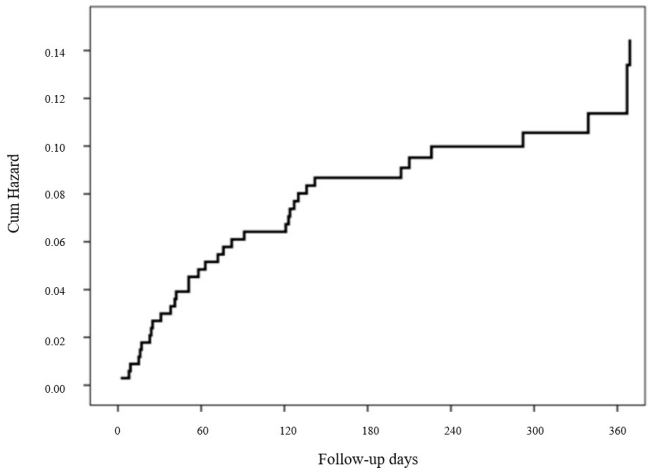

Figure 5. Cox Regression analysis for hazard function of patients who underwent lung resection due to non-small cell lung cancer.

Discussion

This study showed that indices of systemic inflammation in patients with NSCLC, namely NLR and PLR, were significantly decreased immediately after tumor resection. After removal of the tumor tissue, whether the tumor was small (< 5cm) or larger (≥ 5cm), the decrease in blood biomarker levels, including NLR, PLR, were similar. We also determined the NLR cutoff value immediately following tumor resection to be 12 for a two-fold increase in long-term mortality risk.

Hanahan et al showed the prognostic importance of a pro-inflammatory tumor microenvironment [17], and further studies defined the evidence of interaction between inflammatory cells and the growing tumor tissue [18] and showed that increased PLR, NLR, CRP values had prognostic significant correlated to cancer spread [19]. In the present study, we showed that NLR, PLR, and PLT/MPV values, but not CRP, were decreased the day after removal of the NSCLC tumor. These findings support the theory that these inflammatory biomarkers are elevated by the growing tumor tissue. The change in the studied biomarkers pre- and post-surgery were similar whether the tumors were > or < 5 cm. However, apart from NLR, all the other biomarkers (PLR, PLT/PMV, CAR, and CRP) had a significantly higher level in those cases with tumors ≥ 5 cm compared with those with tumors < 5 cm. Although changes in both PLR and NLR were well correlated, there was no meaningful correlation with tumor size and NLR; the

only statistically significant correlation found relative to tumor size was in the case of pre-operative PLR and PLT/MPV. Pre-operative biomarker values were similar in females and males, however, after surgery, females showed a more significant decrease in NLR. A recent meta-analysis suggested that an elevated CAR was indicative, not only of sepsis, but also of unfavorable clinico-pathological findings in solid tumors [16]. In the present study, although unchanged after surgery, CAR values were nearly three times higher in the bigger tumor size group. CAR values may not be as quickly changed due to serum albumin being a chronic clinical state biomarker and may need time to normalize.

A recent meta-analysis evaluated pretreatment (either chemotherapy or surgery) NLR in patients with NSCLC. This meta-analysis showed that elevated NLR was associated with a poor prognosis in terms of overall survival and progress-free survival [9]. It also showed that elevated NLR indicated a worse prognosis in NSCLC patients' treated with chemotherapy compared with surgery. The authors advised further study to clarify the effect with surgery [9]. The results presented in the current study indicate the potential prognostic usefulness of NLR values in patients with NSCLC. We revealed that after lung resection, patients with NLR values over 12 had a two-fold mortality rate in the six-month follow-up period. In the previously cited meta-analysis NLR values were between 2.5 to 5 [9]. Tomita and coworkers studied a similar patient population that included 284 NSCLC patients who received a lung resection, either lobectomy or pneumonectomy and were followed for a five-year period. They defined five-year survival factors and showed that NLR values greater than 2.5 increased the mortality risk [14]. Pinato et al looked at NLR and PLR biomarkers in 220 patients with NSCLC who underwent lung resection and they revealed that an NLR value of five had an unfavorable prognostic significance. In the present study, the Cox regression model showed that a NLR value of five was not correlated with six-month mortality in patients with NSCLC. Sarraf et al assessed the correlation of NLR values with prognosis in 177 patients with NSCLC who underwent lung resection [11]. In their study, the median (IQR) NLR values of all patients was 3.13 (2.08–4.36) and the hazard ratio of each increased NLR for long term survival was 1.10. In the present study the median NLR value was nearly five times greater than Sarraf's study.

The strength of this study was that all the data were obtained from an electronic hospital database thus preventing data entry errors. The limitations were firstly that this was a retrospective, single center study. However, the study center is a specialized in chest and thoracic surgery and is the biggest center of its kind in the country, indicating that the results may be meaningful for clinicians. The second limitation is that the follow-up period of six months was not long enough and the number of deaths during the follow-up period was relatively small (n = 36) potentially resulting in an underestimation of prognostic predictors. Nonetheless, the primary concern of the study was to determine acute changes in biomarkers post-surgery, and their value as prognostic predictors.

In conclusion, immediately after tumor resection, NLR, PLR, and even PLT/MPV were decreased, supporting the direct relationship of these biomarkers with the tumor. Tumor size tended to increase the level of studied biomarkers to some extent. The decrease in biomarker values post-resection was independent of the size of the tumor. A NLR > 12 post-lung resection may be an important prognostic value for long-term (six-month) mortality. NLR and PLR may be helpful biomarkers for NSCLC, both after surgery and during long-term follow-up.

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Declaration of conflicting interests

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Original Article

Primary pulmonary carcinosarcomas: postoperative results and survival analysis

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ABSTRACT

Background: In this study, we assessed the long-term results of 11 patients that we operated due to primary pulmonary carcinosarcoma in the light of literature.

Materials and Methods: We analyzed 11 patients' data, who underwent lung resection, retrospectively between 2009-2018. The comorbidity score was calculated according to the modified Charlson Comorbidity Index (CCI).

Results: Of the 11 patients in the study, 10 (90.9%) were male, one was female (%9.1), and the median age of the subjects was 59.18 ± 8.86. Nine of the patients (81.8%) underwent lobectomy, two of them (18.1%) underwent pneumonectomy. As a cellular type, 6 of them have squamous cell carcinoma, 5 of them have adenocarcinoma. Furthermore, as a sarcomatous component, we detected 6 of the patients have spindle cell sarcoma, 3 of them have chondrosarcoma, one of them has osteosarcoma. and one patient has angiosarcoma. Nine complications occur postoperatively in 5 patients (45.9%). The five-year survival rate was 36.4%. Patients who received adjuvant chemotherapy, the five-year survival rate was 50%, meanwhile, patients who did not receive adjuvant chemotherapy five-year survival rate was not detected (P = 0.006). If the patients have CCI score is two and below their five-year survival rate was 44.4%, meanwhile if the patients have CCI score is two and above their five-year survival rate was not detected (P = 0.018). Recurrence or metastasis was diagnosed in 7 patients (63.6%) postoperatively. The 5-year disease-free survival rate is 12.5%.

Conclusions: Surgical resection is still the most effective treatment modality for these patients. Adjuvant therapy and comorbidity are detected most important factors that affect the survival rate.

Keywords: carcinosarcoma, survival, surgery, lung

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Introduction

Primary pulmonary carcinosarcomas (PPCs) are rare malignant tumors of the lung and account for less than 1% of overall lung malignancies [1,2]. Kika et al first described these tumors as sarcomas containing poorly differentiated non-small cell carcinoma [3].

Pulmonary carcinosarcomas are commonly seen in middle-aged men and are associated strongly with smoking. The World Health Organization classifies these malignancies under the subgroup of sarcomatoid carcinomas, and they have a poorer prognosis than do non-small cell lung carcinomas [4,5]. Preoperatively, diagnostic and interventional procedures are limited. In non-metastatic diseases, the gold standard for treatment is complete surgical resection, which is also a diagnostic procedure. Few reports have described patients with PPC who underwent surgery, and the studies in which these patients were included were conducted with small samples [6,7]. At this time, PPCs are believed to behave like sarcomas. In this study, we evaluated long-term results from 11 patients who underwent surgery for PPC based on previous reports.

Materials and Methods

A patient database including those who underwent lung resection due to carcinosarcoma was created prospectively between January 2009 and December 2018, and this database was evaluated retrospectively in this study. Data from 11 subjects were included. We could not access data on one patient; thus, we excluded that patient from the study. Comorbidity scores were calculated according to the modified Charlson Comorbidity Index (CCI) [8]. The study was approved by the institutional review board (No: 2020/2251) and was conducted in accordance with the principles of the Declaration of Helsinki.

Patient selection

All patients were evaluated preoperatively with thoracic tomography. To detect distant metastasis, PET/CT and cranial magnetic resonance imaging were performed (Figure 1).

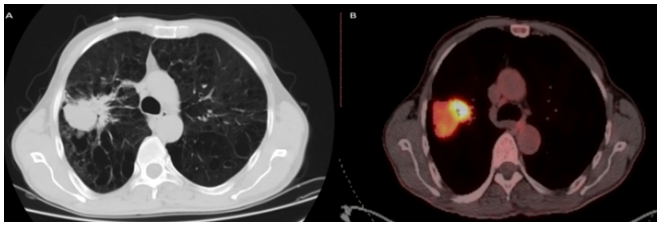

Figure 1. (a) Thoracic CT image of a lesion in the right upper lobe, **(b)** PET/CT image of the lesion in the right upper lobe, showing increased FDG uptake.

The pulmonary reserve was determined based on pulmonary function tests. When the forced expiratory volume in the first second was ≤ 40%, we ordered a carbon monoxide diffusion test and lung perfusion scintigraphy. For patients aged > 60 years and those with histories of cardiac problems, consultation with cardiologists and echocardiographic evaluation was performed. Before the operation, endobronchial lesions were evaluated using fiberoptic bronchoscopy. The preoperative mediastinal staging was performed according to the European Society of Thoracic Surgeons and American Thoracic Society guidelines [9].

Postoperative follow-up

Data on morbidities occurring during hospitalization, including hemorrhage, persistent air leakage, atrial fibrillation, pneumonia, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and septicemia, were collected. Persistent air leakage was diagnosed when leakage lasted ≥ 7 days. Data on mortality occurring during hospitalization, including intraoperative death, and within 3 months following surgery were collected.

Data on patients' demographic characteristics, morbidity, duration of hospitalization, mortality, histopathological characteristics, and development of relapse, as well as 5-year survival rates, were analyzed. Patient data, including age, comorbidities, tumor histopathology, tumor stage, adjuvant therapy, induction therapy, and survival, were obtained from hospital records and the national survival database. Patient follow-up included thoracic CT and physical examination, performed together with oncologists. Patients were examined every 3 months for the first 2 years, every 6 months in years 2-5, and annually thereafter.

Statistical Analysis

The chi-squared test and Fisher's exact test were used to examine relationships among patients' demographic, clinical, descriptive, and categorical data. For continuous variables, we used Student's t-test, the Mann–Whitney U test, and Kruskal-Wallis analysis. Kaplan-Meir analysis was used to examine patient survival. To identify factors affecting survival, we used the log-rank test. The significance level was set at $p < 0.05$. All statistical analyses were performed with the SPSS software package (version 22; SPSS Inc., Chicago, IL, USA).

Results

The sample for this study comprised 10 (90.9%) male patients and one (9.1%) female patient. The patients' median age was 59.18 ± 8.86 years. Nine (81.8%) patients were aged < 65 years and two (18.2%) patients were in the geriatric age group. The average smoking history was 23.54 ± 8.71 pack-years. The most common symptoms in these patients were coughing (54.5%) and dyspnea (36.3%). One (9.1%) patient was asymptomatic. Six patients had tumors on the right lung and five had tumors on the left lung. Six patients were diagnosed preoperatively, with sarcomatoid carcinoma (n = 1 (9.1%)), malignant mesenchymal tumors (n = 3 (27.2%)), and small round cell malignant tumors (n = 2 (18.1%)). Four (36.3%) patients were diagnosed preoperatively based on the detection of endobronchial lesions. All patients underwent thoracotomy with a posterolateral approach. Nine (81.8%) patients underwent lobectomy and two (18.1%) patients underwent pneumonectomy. Patients' demographic characteristics are summarized in Table 1.

Table 1. Demographic characteristics of the patients.

Variables		N	%
Gender	Male	10	90.9
	Female	1	9.1
Age (Year) Mean±StD		59.18±8.86	
Age	<65	9	81.2
	>65	2	18.2
Smoke (Packet/year) Mean±StD		23.54±8.71	
CCI	0	5	45.5
	1	3	27.3
	2	1	9.1
	3	1	9.1
	6	1	9.1
Side	Right	6	54.5
	Left	5	45.5
Preoperative diagnosis	No	5	45.5
	Yes	6	54.5
Operations	RUL	4	36.4
	RLL	1	9.1
	RLBL	1	9.1
	LUL	2	18.2
	LLL+diaphragm and chest wall resection	1	9.1
	LP	2	18.2

Abbrev.: CCI: Charlson Comorbidity Index, StD; Standard Deviation, RUL; right upper lobectomy, RLL; right lower lobectomy, RLBL; right lower bilobectomy, LUL; left upper lobectomy, LUL; left lower lobectomy, LP; left pneumonectomy.

The average tumor diameter was 6.53 ± 5.13 cm (range, 2.20–20 cm). According to tumor size, four (36.4%) cases were designated as stage T1, one (9.1%) as stage T2, two (18.2%) as stage T3, and four (36.4%) as stage T4. Ten of the 11 cases were graded as N0 and one case was graded as N1 during the postoperative period. Five (45.4%) cases were classified as TNM stage IIIA, one (9.1%) as stage IIB, and five (45.4%) as stage I. Histopathologically, six (54.5%) cases were determined to be squamous cell carcinoma (SqCC) and five (45.4%) cases were determined to be adenocarcinoma. Sarcomatous components were spindle cell sarcoma [n = 6 (54.5%)], chondrosarcoma [n = 3, (27.2%)], and osteosarcoma [n = 1 (9.1%)]. One (9.1%) patient had angiosarcoma (Figure 2).

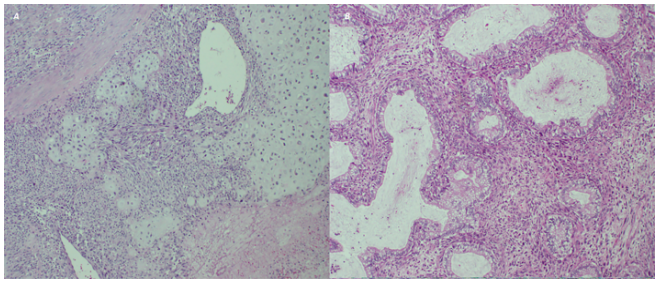

Figure 2. (a) Chondrosarcomatous component of a tumor (Hematoxylin and eosin stain, ×200), **(b)** Adenocarcinomatous component of a tumor with an acinar structure (Hematoxylin and eosin stain, ×200).

In total, nine postoperative complications in five (45.9%) patients were recorded. One patient who underwent pneumonectomy presented postoperatively with atrial fibrillation, which could be treated medically. Hemorrhage (400 cc/day) occurred postoperatively in two patients, but did not necessitate revision. Two patients had persistent air leakage; one healed spontaneously and the other was treated with blood patch pleurodesis. One patient developed ARDS after AKI; septicemia occurred and the patient died. Two patients had pneumonia that could be treated medically.

Two deaths occurred within 90 days postoperatively. One patient died because of ARDS, AKI, and sepsis; the other patient died of myocardial infarction while under adjuvant therapy. Postoperative adjuvant therapy was administered to eight patients; one patient died in the early postoperative stage and did not receive such

therapy, and two patients had poor general medical conditions precluding it.

The average follow-up period for patients who underwent surgery was 31 months. The median survival duration was 51.1 ± 14.6 months (95% confidence interval (CI), 10.5-51.5 months) and the 5-year survival rate was 36.4% (Figure 3).

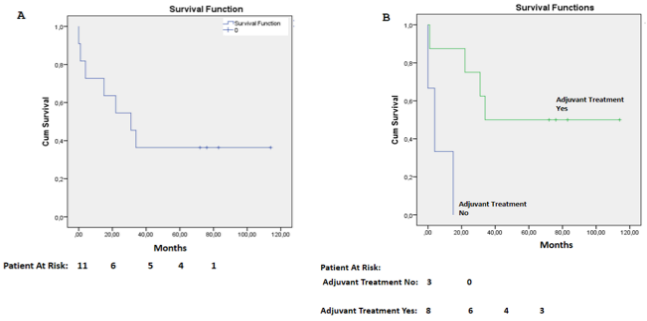

Figure 3. Kaplan–Meier curves, **(a)** overall survival, **(b)** adjuvant treatment.

For patients who received adjuvant therapy, the 5-year survival rate was 50%; for those who did not receive adjuvant therapy, the 5-year survival rate was not detected (P = 0.006). The 5-year survival rate for patients with CCI scores ≤ 2 was 44.4%; this rate was not detected for patients with CCI scores > 2 (P = 0.018). Table 2 shows the factors that affected the survival rate. Recurrence or metastasis was detected postoperatively in 7 (63.6%) patients. The average disease-free survival (DFS) period was 18 months (95% CI, 6–29 months) and the 5-year DFS rate was 12%.

Discussion

Pulmonary carcinosarcomas are poorly differentiated biphasic tumors with epithelial and mesenchymal components. These tumors are rare and are considered to form a subgroup of pulmonary sarcomatoid carcinomas [10–12]. PPCs commonly present in men with smoking histories. Huwer et al. [13] reported that 71.4% of

Table 2. Factors that affect the survival rate.

Variables		5 year survival (%)	Median survival (months)	%95 (CI)	P
Age	<65	44.4	57	23-90	0.542
	>65	0	24	5-43	
CCI	0-2	44.4	34	31-92	0.018
		0	1	0-5	
Side	Right	33.3	31	0-65	0.797
	Left	40	22	0-61	
N status	pN0	40	31	24-85	0.353
	pN1	0	15	15-15	
T stage	1	75	85	37-133	0.480
	2	0	22	22-22	
	3	0	17.5	0-49	
	4	25	31	4-58	
Tumor diameter	< 7cm	42.9	34	3-64	0.630
	> 7cm	25	15	0-41	
Adjuvant treatment	No	0	4	0-15	0.006
		50	34	35-100	

Abbrev.: CCI; Charlson Comorbidity Index, CI; Confidence Interval.

patients in their sample were men. According to previous reports, pulmonary carcinosarcoma is four to seven times more common in men than in women [7,10,14,15]. In our sample, 91% of the patients were men and most of them were active smokers.

PPCs are more common on average in 60-year-olds and present in three main clinical forms, with endobronchial, peripheric or parenchymatous, or both parenchymal and endobronchial components. Depending on disease location, patients show symptoms such as coughing, dyspnea, hemoptysis, chest pain, fatigue, and loss of weight, or are asymptomatic [16,17]. Tastepe et al. [15] noted that the tumors were located peripherally in 85.7% of cases and that the most common symptom was coughing (57%). Similarly, Sokucu et al. [10] noted that the most common symptom was coughing (66.6%). Koss et al. [18] reported that the tumors were

located peripherally in 62% of patients and that symptoms included coughing, dyspnea, and hemoptysis. In our study, 54.5% of tumors had peripheric/parenchymal and endobronchial components and the most common symptoms were coughing (54.5%) and dyspnea (36.3%). One (9.1%) of our patients was asymptomatic.

Preoperatively diagnosed pulmonary carcinosarcoma cases are rare. Davis et al. [19] reported that all of the 17 patients in their sample were diagnosed preoperatively with malignancy, but that only two (11.7%) were diagnosed with carcinosarcoma based on fine-needle aspiration. Similarly, Braham et al. [20] reported that patients were diagnosed preoperatively with non-small cell lung cancer. Devi et al. [17] reported that preoperative biopsies resulted in the diagnosis of poorly differentiated carcinoma. Our findings suggest that the most important factors affecting diagnosis are the biphasic and poorly differentiated nature of the tumors.

Immunohistochemical evaluation of these tumors results in the detection of SqCC as an epithelial component [5,10,15,18,21,22]. Koss et al. [18] noted that epithelial components of these tumors are primarily SqCC (46%) and adenocarcinoma (31%). Tastepe et al. [15] identified SqCC in four (57%) patients and adenocarcinoma in two (28.5%) patients. The most common sarcomatous components are poorly differentiated chondrosarcoma, osteosarcoma, and rhabdomyosarcoma [18,21,23]. Similarly, we detected SqCC as an epithelial component in six (54.5%) patients in our sample. In contrast to previous reports, we detected spindle cell sarcoma in six (54.5%) patients and chondrosarcoma in three (27.2%) patients as sarcomatous components.

Surgical resection is the optimal treatment modality for non-metastatic pulmonary carcinosarcoma. Case series exploring systemic treatment are limited, and the superiority of chemotherapy and radiotherapy to surgery remains controversial [1]. On the other hand, systemic treatment has been successful in part in patients who are not eligible for surgery. Langer et al. [24] reported a period of partial tumor regression and a median survival duration of 9 months in patients with pulmonary carcinosarcoma and chronic obstructive pulmonary disease who received cisplatin + etoposide. However, they detected distant metastasis a few months later. Ersek et al. [1] reported median survival duration of 20 months for patients who underwent surgery alone, 4 months for those who received radiotherapy, and 7 months for those treated with surgery and radiotherapy ($p < 0.001$). We prefer surgical treatment to systemic treatment for patients with PPC; because of the poorly differentiated and aggressive nature of these tumors, however, the prognosis is poor, with reported survival rates ranging from 20% to 57% [7,10,15,18,25]. Sokucu et al. [10] reported a median survival duration of 9 months. Koss et al. [18] demonstrated that small tumor diameter and early disease stage are good prognostic factors, and reported a 5-year survival rate of 21.3%. Davis et al. [19] reported a 2-year survival rate of 25%, and Xu et al. [25] reported a 2-year survival rate of 43%. In our study, the 5-year survival rate was 36.4%, and the CCI score and adjuvant therapy affected prognosis. Differences in survival rates are due to the examination of small patient populations and differences in the histopathological characteristics of tumor cells (especially in sarcomatous components [13], disease stage, and postoperative treatment modalities.

Postoperative complications occurred in five (45.4%) patients in our sample. The most common complications were persistent air leakage and pneumonia that responded to medical treatment, which occurred in two (18.1%) patients each. These complication rates are higher than reported previously. They were higher in patients with comorbidities, larger tumors, and longer smoking histories. Tastepe et al. [15] reported persistent air leakage in two (28.5%) patients in their sample. Petrov et al. [7] reported minor complications in two patients and bronchopleural fistula (BPF) in one (20%) patient. Sokucu et al. [10] detected BPF in two (33.3%) patients. These reports, however, are case studies with limited numbers of patients.

Postoperative adjuvant therapy improves the prognosis of PPC [10,15,19,25]. Xu et al. [25] reported that chemoradiotherapy improved the 5-year survival rate in five (33.3%) patients. In our study, the 5-year survival rate for patients who received adjuvant therapy was 50% ($p = 0.006$). We recommend adjuvant therapy during the postoperative period, but further studies of the effects of such therapy are needed.

High pulmonary carcinosarcoma recurrence rates have been reported. Huwer et al. [13] detected local or distant organ metastasis in six (85.7%) patients. Koss et al. [18] reported recurrence in 25 (37.8%) patients, most commonly in the lymph nodes. In contrast, Tastepe et al. [15] reported distant organ recurrence in only one (14.2%) patient. We detected local or distant metastasis or recurrence in seven (63.6%) patients in our sample. The DFS duration was 18 months, and the 5-year DFS rate was 12.5%. As PPCs are biphasic, aggressive, poorly differentiated tumors that behave like sarcomas, the recurrence rate of these tumors is high.

Limitations of this study are its retrospective design and the inclusion of a small number of patients, especially women, may have resulted in bias. Because of the small patient population, a multivariate analysis could not be performed.

In conclusion, as PPCs are rarely diagnosed preoperatively, due primarily to the wide range of variation in their histopathological structure, surgical resection remains the most effective treatment modality. Adjuvant therapy and comorbidities are the most important factors affecting the survival rate. Nevertheless, prognostic factors for these carcinosarcomas have not been identified. Thus, further prospective multicenter studies are needed.

Declaration of conflicting interests

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Original Article

The relationship of platelet lymphocyte ratio with prognosis in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: The aim of this study is to analyze prognostic biomarkers, and determine the biomarkers which are more sensitive in the patients that were presented with acute chronic obstructive pulmonary disease (COPD) exacerbation to the emergency department.

Materials and Methods: The data of 243 patients presented with acute COPD exacerbation and 122 COPD patients with stable status as control group were analyzed retrospectively. The patients, whose arterial blood gas (ABG) studied, with Acute COPD exacerbation were identified as Group I. The patients whose venous blood gas (VBG) studied were identified as Group II and stable COPD patients whose ABG studied were identified as Control Group. The prognostic biomarker values were compared in the patients of Group I, Group II and Control Group

Results: The mean age of the patients was 68.61 ± 11.02 and the mean age of the control group was 68.25 ± 11.07. It was found that platelet lymphocyte ratio (PLR) values were very high in both Group I and Group II compared to the control Group ($P < 0.001$). There was a significant difference related with mean erythrocyte distribution width (RDW) in Group I, mean erythrocyte volume (MCV)' in group II, MPV and platelet count (PLT) in both Group I and Group II ($P < 0.001$).

Conclusions: Especially in acute COPD exacerbation, PLR may be a useful inflammatory biomarker to reflect the severity and activity of inflammation in COPD patients.

Keywords: chronic obstructive pulmonary disease, biomarker, platelet-lymphocyte ratio, emergency department

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Introduction

COPD affects more than 5% of adult population and causes approximately 2,75 million deaths each year [1]. Also it is the third leading cause of death worldwide [2-4]. COPD is a progressive disease affecting lung parenchyma and peripheral airways, systemically effective with chronic inflammation and widespread with progressive airflow limitation and its attacks can be treated [2-6]. Abnormal inflammatory response and phenotype properties of lungs against harmful gases or particles reinforce the view that systemic inflammation occurs [7]. Recently researchers have found a relationship between systemic inflammation and platelets. It has been shown that platelets play an important role in the pathogenesis of inflammation, thrombosis and atherogenesis by interacting with endothelium, leukocytes or liberating mediators [8,9]. It has been studied with many types of biomarkers, particularly related to platelets, which can be used to detect the prognosis of COPD. PLT, mean platelet volume (MPV), platelet distribution width (PDW), PLR, MCV, RDW [10]. In literature, these biomarkers have been studied separately in patients with acute COPD exacerbation. However, we could not find any studies that examined these biomarkers in COPD patients at the same time and compared the results of which were more sensitive.

The aim of this study is to compare the biomarker values of the patients presented with acute COPD exacerbation in emergency service to the biomarker values of stable COPD patients, to determine the biomarker which is more sensitive for COPD and to investigate the difference status according to gender.

Materials and Methods

This study was carried out in Van Yuzuncu Yıl University, Faculty of Medicine Emergency Department between October 2016 and April 2017. It is a retrospective study. The data were taken from the hospital information system. Criteria for inclusion in the study; patients diagnosed with COPD older than 18 years. Exclusion criteria; patients with heart failure, kidney failure, cancer history, primary valve heart disease, connective tissue diseases, inflammatory bowel disease, liver diseases and hematological system diseases were not included in the study. The files of 861 patients who applied to the emergency department with the complaint of dyspnea due to acute COPD exacerbation were analyzed. According to exclusion criteria, 243 patients were included in the study. The patient group with arterial blood gas (ABG) (n = 100) was taken as group II, the patient with venous blood gas (VBG) (n = 143). 122 patients with COPD registered in the hospital system and whose condition was stable were included in the study as a control group (n = 122). Prognostic biomarkers; PLT, PLR, MPV, MCV, RDW were determined. Biomarker values of Group I, Group II and control Group were compared. Correlation values were investigated. Analysis was made according to gender. This study was approved by the institutional ethics committee of Van Yuzuncu Yıl University (B.30.2.YYU.0.01.00.00/43).

Statistical Analysis

Descriptive statistics for the studied parameters were presented as mean, standard deviation, minimum and maximum values. One-way ANOVA was performed for the comparison of group means. Following One-Way Variance Analysis, Duncan multiple comparison test was also used to determine different groups. For determination linear relationships among the parameters, Pearson correlation analysis was carried out in each group. The significance level was set at $P < 0.05$. All statistical analyses were performed with the SPSS software package (version 21; SPSS Inc., Chicago, IL, USA).

Results

The mean age of 243 patients with acute COPD exacerbation was 68.61 ± 11.02, it was 117 (48.15%) males and 126 (%51.85) females. The mean age of 122 patients in Control Group was 68.25 ± 11.07, 61 (50%) males and 61 (50%) females. The biomarker values of patients in Group I and Group II were compared with those of the Control Group. Compared to the Control Group, a relatively high difference was detected about PLR in both Group I and Group II patients with acute COPD exacerbation ($P < 0.001$). A significant difference for RDW in Group I, MCV in Group II, MPV and PLT in both Group I and Group II was investigated ($P < 0.001$) (Table 1).

Correlation values of the biomarkers compared to the Control Group; RDW was found to be negatively correlated with MCV, MPV was negatively correlated with MCV and

Table 1. Descriptive statistics and comparison results of the groups for the parameters.

		N	Mean	Std. Dev.	Min.	Max.	P
Age (years)	Group II	143	68.01	10.708	27	94	0.571
	Group I	100	69.48	11.470	38	94	
	Control	122	68.25	11.214	39	98	
	Total	365	68.49	11.077	27	98	
MCV (fl)	Group II	143	85.613 ab	7.479	65.7	103.9	0.022
	Group I	100	87.249 a	7.433	62.9	103.2	
	Control	122	84.459 b	7.429	61.6	101.5	
	Total	365	85.675	7.508	61.6	103.9	
RDW (%)	Group II	143	18.083 a	3.982	13.2	31.4	0.001
	Group I	100	16.775 b	3.300	12.6	29.5	
	Control	122	16.348 b	3.270	12.5	29.7	
	Total	365	17.145	3.647	12.5	31.4	
PLT (103/ μL)	Group II	143	229.26 b	80.377	27	465	0.002
	Group I	100	215.97 b	93.666	29	581	
	Control	122	255.31 a	78.631	63	505	
	Total	365	234.33	84.923	27	581	
MPV (fl)	Group II	143	8.925 a	1.201	6.5	14.3	0.001
	Group I	100	9.083 a	1.356	6.9	14.6	
	Control	122	8.479 b	1.103	6.6	13.9	
	Total	365	8.819	1.237	6.5	14.6	
LY1 (103/ μL)	Group II	143	1.512 b	1.348	0.2	9.7	0.001
	Group I	99	1.408 b	1.097	0.2	7.5	
	Control	122	21.520 a	10.047	1.9	51.4	
	Total	364	8.190	11.158	0.2	51.4	
PLR	Group II	143	240.139 a	183.386	3.65	1135.00	0.001
	Group I	99	233.505 a	178.546	15.87	793.33	
	Control	122	17.675 b	22.177	1.65	186.84	
	Total	364	163.773	180.895	1.65	1135.00	

a, b: Different lower cases represent statistically significant differences among the groups for each parameter ($P < 0.01$).
Abbrev.; MCV: mean corpuscular volume; RDW: red cell distribution; PLT: platelets; MPV: mean platelet volume; LY1: lymphocytes; PLR: platelet-to-lymphocyte ratio.

Table 2. Pearson correlation coefficients for the parameters in group I.

	Age	MCV	RDW	PLT	MPV	LY1	PLR
Age (year)	1						
MCV (fl)	0.126	1					
RDW (%)	-0.278**	-0.438**	1				
PLT (103/ μL)	-0.118	-0.075	-0.185	1			
MPV (fl)	0.095	-0.180	0.289**	-0.428**	1		
LY1 (103/ μL)	-0.054	-0.109	-0.112	0.142	-0.124	1	
PLR Ratio	0.011	-0.007	0.066	0.206*	-0.086	-0.600**	1

**: $P < 0.05$; **: $P < 0.01$.*
Abbrev.: MCV: mean corpuscular volume; RDW: red cell distribution; PLT: platelets; MPV: mean platelet volume; LY1: lymphocytes; PLR: platelet-to-lymphocyte ratio.

Table 3. Pearson correlation coefficients for the parameters in group II

	Age	MCVfl	RDW	PLT103μL	MPVfl	LY1103μ	PLR
Age (year)	1						
MCV (fl)	0.126	1					
RDW (%)	-0.119	-0.676**	1				
PLT(103/ μL)	-0.054	-0.100	-0.088	1			
MPV (fl)	0.013	-0.192*	0.256**	-0.394**	1		
LY1 (103/ μL)	0.092	0.105	-0.010	0.152	-0.026	1	
PLR Ratio	0.022	-0.254*	0.104	0.057	-0.099	-0.545**	1

**: P < 0.05; **: P < 0.01.*
Abbrev.: MCV: mean corpuscular volume; RDW: red cell distribution; PLT: platelets; MPV: mean platelet volume; LY1: lymphocytes; PLR: platelet-to-lymphocyte ratio.

PLT, and positively correlated with RDW (Tables 2,3). Correlation values in Group are as follows; RDW showed a significant negative correlation with age and MCV, and a significant positive correlation with MPV and PaCO2 in Group I. In Group II, RDW showed a significant correlation with MCV, a significant correlation with MPV and PaCO2 (Table 4).

We investigated whether there is a significant difference in biomarkers between groups according to gender. A significant difference was found between men and women in MCV (P = 0.03) and MPV (P = 0.04).

Table 4. Pearson correlation coefficients for the parameters in control group.

	Age	MCV	RDW	PLT	MPV	LY1	PaCO2	PLR
Age (year)	1							
RDW (%)	0.016	-0.717**	1					
PLT (103/ μL)	-0.001	-0.064	-0.060	1				
MPV(fl)	0.018	-0.373**	0.240**	-0.232**	1			
LY1(103/ μL)	-0.111	0.161	-0.194*	-0.111	-0.070	1		
PLR Ratio	0.106	-0.079	0.039	0.377**	0.046	-0.566**	-0.138	1

**: P < 0.05; **: P < 0.01.*
Abbrev.: MCV: mean corpuscular volume; RDW: red cell distribution; PLT: platelets; MPV: mean platelet volume; LY1: lymphocytes; PLR: platelet-to-lymphocyte ratio.

Discussion

The key findings in the study on biomarkers and blood gas used to determine severity and prognosis of COPD are; PLR values in Group I and Group II increased significantly compared to the Control Group in Acute COPD exacerbation. According to data in literature; platelets can lead various systemic inflammatory conditions by releasing different cytokines and mediators while playing an active role in the immune system [11]. In this study, increasing of PLR value derives from the increase in platelet number and decrease in lymphocyte number in an inflammatory. It is a useful biomarker to reflect the severity and activity of inflammatory in the COPD patients especially during acute exacerbation. When Kurtipek et al. compared PLR values between the patients with acute COPD exacerbation and the ones with stable COPD, they found that PLR value was significantly high in the patients with acute COPD exacerbation. Actually they found that the number of lymphocyte in peripheric blood was inversely correlated with inflammation in body and therefore PLR was associated with poor outcomes in the COPD patients [12] Kumar et al. found that PLR was associated with 90-day mortality increase of patients with Acute COPD exacerbation in their studies. PLR is prognostically a new scientific contribution in chronic inflammatory disorders

such as COPD [13]. The most important cause of high PLR value is the very low number of lymphocyte in acute COPD exacerbations. In this study, a considerable decrease in the number of lymphocyte was found in the COPD patients during acute exacerbations. Results of the study are consistent with both acute exacerbation and prognostic data in literature.

In the studies according to the GOLD categories of COPD, they show that RDW levels are associated with increased mortality risk. In their studies, Tertemiz et al. showed that high RDW levels were associated with severity of disease and low survival rates in COPD patients [14]. Seyhan et al. think that RDW may be high due to inflammation and oxidative stress and therefore high RDW levels may reflect an inflammatory condition in COPD patients. Thus, RDW level is one of the most important factors showing mortality [15]. Kalemci et al. showed that RDW and PDW values were independently related to the severity of COPD in another study [10]. Ozgul et al. determined that RDW levels in COPD patients were significantly higher than in healthy individuals in their studies [16]. As stated in these results, RDW became more prominent. However, PLR value has been found to be more prominent in our study. When RDW values in Group I and Group II were compared to the ones in the Control Group, it was determined that there was a significant difference in Group II, but not in Group I. RDW values in Group I and Group II were negatively correlated with MCV values and the results in our study were partially consistent with data in literature.

MPV value is one of the platelet function indices showing the platelet production rate and stimulation. In a literature survey by Ulasli et al. investigated that MPV decreased during COPD exacerbation compared to stable period and the Control Group [17]. Decrease in MPV values may show increased systemic inflammation during COPD exacerbation, therefore MPV can be used as a negative acute phase reactant during acute COPD exacerbation. However, Makhouf et al. reported that MPV and PDW values in COPD patients were significantly higher than in Control Group [18]. Steiropoulos et al. reported that MPV and WBC levels in the COPD patients were higher than in smokers having normal respiratory function; hence, there may be vascular risk together with COPD [1]. In this study MPV values were found to be high in acute COPD exacerbations. Measurements of variances in MPV during follow-up can be considered as a rapid and reliable tool in the assessment of inflammatory responses. These results show platelet activation and increased systemic inflammation in COPD patients. In a study by Karadeniz et al. showed a higher platelet number in COPD patients during acute exacerbation [19]. The study by Harrison et al. reported that there was a significant increase in thrombocytosis of the patients with acute COPD exacerbation in one-year. They stated that thrombocytosis caused a significant increase especially in hospital mortality, and it was correlated with the symptoms of type II respiratory failure and severity of exacerbation [20]. Chen et al. investigated that inflammatory biomarkers observed in routine blood tests can widely be used as differential diagnosis and prognostic assessment factors in many cases such as inflammatory diseases, cancer and cardiovascular diseases [21].

The limitation of this study was the low number of patients and its retrospective nature.

In conclusion, since the elevation of PLR in an inflammatory condition reflects the increase in platelet number and the decrease in lymphocyte, it is a useful inflammatory biomarker to reflect the severity and activity of inflammation particularly during acute exacerbation in COPD patients. In this study, PLR is more sensitive than other biomarkers used in the treatments and follow-up of the prognosis of COPD patients. Thus, PLR can be used as a biomarker in the follow-up of acute COPD exacerbation in emergency departments.

Declaration of conflicting interests

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Original Article

Rare and unusual tracheobronchial foreign bodies

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ABSTRACT

Background: Foreign body aspirations are rare in adults but are common in children between the ages of 0-3. Clinically, cough is the most common complaint. Delays in diagnosis can cause complications in the lower respiratory tract and lung parenchyma. This study aimed to offer a reminder that rare and unusual foreign bodies may be the cause of tracheobronchial aspiration and to present the surgical approach.

Materials and Methods: Patients who were admitted to our outpatient clinic or who were referred by other clinics for foreign body aspiration between January 2012 and January 2017 were retrospectively analyzed. Foreign objects such as coins, food pieces, toy pieces, and needles, which were routinely encountered, were excluded from the study. Gender, age, complaints, radiological findings, and surgical interventions were recorded.

Results: There were five cases (four males, one female) under the age of 18 and three male cases above the age of 18. The average age was 21.18 ± 28.93. There was one case with laryngectomy. In six cases, the foreign body was removed by rigid bronchoscopy. Lung resection was performed in three cases (one lobectomy and one wedge resection). The foreign bodies were a pen tip, a piece of stone, a rivet from jeans, the LED of a remote control, a latch spring, a piece of a spoon, a wood piece, and a piece of a dental filling.

Conclusions: Foreign body aspirations are among the most significant causes of morbidity and mortality, especially in the child age group. Diagnosis is possible through anamnesis, physical examination, and evaluation of radiological findings together. In the event of clinical suspicion, foreign body aspirations should be kept in mind regardless of age group.

Keywords: airway management, bronchoscopic surgical procedure, respiratory aspiration.

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Introduction

Most tracheobronchial foreign body aspirations are seen between the ages of 0 to 3 and are responsible for 7% of deaths in this age group [1,2]. The most common symptom is a cough, as if drowning, that continues after aspiration. Foreign body aspiration should be kept in mind in patients with wheezing, chronic cough, hoarseness, or recurrent lung infections. Complications can range from lung abscess to bronchiectasis [3]. Foreign body aspirations in adults are rarely seen in comparison to children [4]. If tracheobronchial foreign bodies are diagnosed in the early period and the foreign body is removed, complications do not develop [5]. Interesting and rare foreign bodies result in vague images directly on the radiograph, and the nature of the aspirated object cannot be revealed easily. Therefore, it is important to present these cases. However, it is striking that, in the literature, such instances are usually presented as case reports.

This study aims to examine interesting foreign bodies in terms of diagnosis and bronchoscopic removal methods, to emphasize that any foreign body can be aspirated in the child age group, and to present interesting foreign body aspirations encountered in adulthood.

Materials and Methods

Eight patients were investigated and treated due to uncommon tracheobronchial foreign body aspirations between January 2012 and January 2017. They were analyzed retrospectively after local ethical committee approval (No: 2020/223). Included patients' gender, age, symptoms of admission, radiological findings, and treatment methods were examined. Food items, toy parts, and needle aspirations - all of which are frequently encountered in children - were excluded from the study.

Patient interventions included anamnesis, physical examination, and radiological examinations. Posteroanterior chest radiographs and computed thorax tomography were used as radiological examinations. In the presence of an object that was not detected radiologically in pediatric patients but that was suspected in anamnesis and physical examination, intervention was performed after families were informed about the relevant risks. All pediatric patients underwent rigid bronchoscopy (Karl Storz™ , Germany) under general anesthesia. In patients presenting with intrathoracic lesions, thorax tomography was performed first. Surgery was performed in accordance with lung pathology.

Results

In our clinic, 85 patients underwent bronchoscopy for tracheobronchial foreign body aspiration between January 2012 and January 2017. Eight of these patients diagnosed with the aspiration of a rare and unusual tracheobronchial foreign body were included in this study. Four of five patients were boys, and one was a girl under the age of 18. There were three male cases above 18 years of age. The average age was 21.18 ± 28.93. In three of the cases, foreign bodies were seen in the right main bronchus (Figure 1), in one case, the foreign body was in the left main bronchus (Figure 2); and in one case, the foreign body was in the vocal cords (Figure 3).

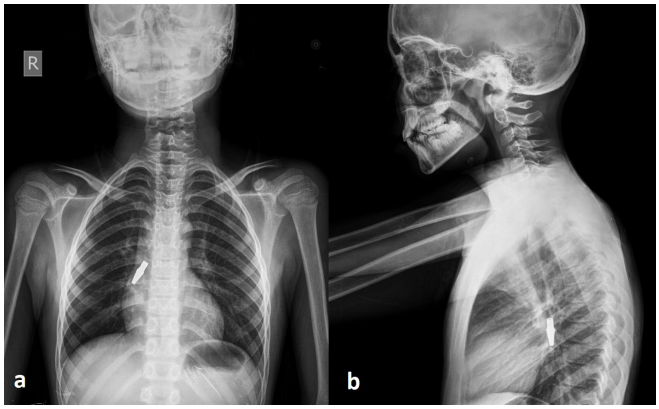

Figure 1. (a) Aspirated pen tip, PA chest x-ray, **(b)** Aspirated pen tip, lateral chest x-ray.

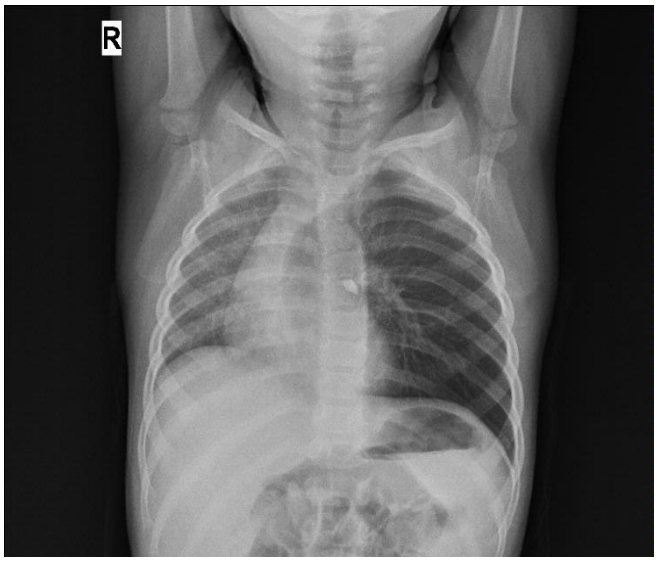

Figure 2. Stone aspiration located in left main bronchus. PA chest x-ray and left obstructive emphysema.

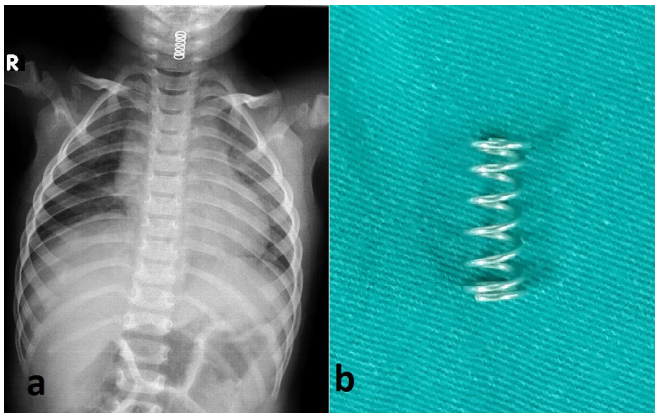

Figure 3. (a) Aspirated latch spring, PA chest x-ray view at the level of vocal cords, **(b)** Removed latch spring.

A foreign body was observed in the right lower lobe of one case with a pulmonary complication, and in more distal of the airway in the left lower lobe of one case (Table 1).

In only three of the cases, the anamnesis finding was a sudden cough; one adult patient admitted to the hospital after noticing aspiration of foreign body. The most common physical examination finding was ronchus. Fever was detected in one case. Although a foreign body history was taken in four cases, the physical examination findings were normal. In five of the cases, foreign bodies were detected by direct radiography due to their metal content (Figure 4).

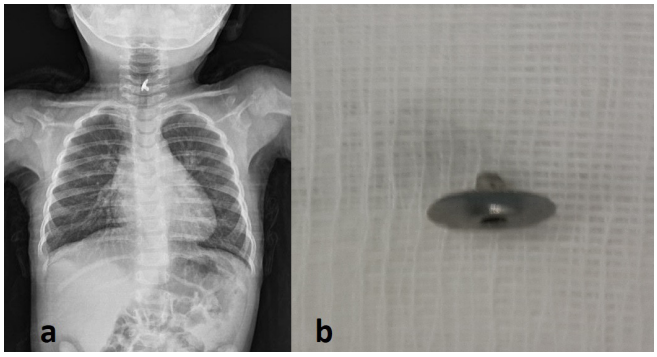

Figure 4. (a) Jeans rivet located in the upper part of the trachea, **(b)** jeans rivet was removed.

Pulmonary consolidation and fibroatelectatic infiltrations were detected in one of two patients who applied with pulmonary complications, while indirect radiological findings were detected in one case. Pneumonia was detected in one patient. A foreign body was detected by bronchoscopy in six of the cases who arrived in the early acute period. In five of all cases in which tracheobronchial foreign bodies detected, the foreign bodies were removed under general anesthesia, while one was removed under local anesthesia by rigid bronchoscopy. Bronchoscopy was performed in five cases within the first eight hours. One of the cases with chronic foreign body aspiration was detected after six years. Left lower lobectomy with thoracotomy was performed in one patient who was admitted with pulmonary complications, while video-assisted thoracoscopic wedge resection was performed in one patient.

Surgical Manipulations

None of the patients developed acute respiratory failure. In six cases, foreign bodies were removed by bronchoscopy no later than 16 hours after aspiration. There was not any patient who underwent bronchoscopy developed pneumothorax in the postoperative period. Chest radiography was performed in each patient in the early postoperative period and 24 hours later. In cases in which patients applied with tracheal foreign body aspiration, and in which bronchoscopy was immediately performed, the foreign body was pushed to the right main bronchus, and the oxygen saturation was increased by ventilating the left lung. In one case, LED lamp wires were first passed through the bronchial orifice and then straightened and removed (Figure 5).

Table 1. Characteristics of the patients.

Patient	Gender	Age	Comorbidity	Foreign bodies	Location
1	M	8 years	No	Pen tip	Right main bronchus
2	M	19 months	No	A piece of stone	Left main bronchus
3	F	17 months	No	Rivet of jeans	Upper trachea
4	M	22 months	No	LED of remote control	Right main bronchus
5	M	20 months	No	Latch spring	Vocal chords
6	M	76 years	Laryngectomy, tracheotomy	A piece of spoon	Right main bronchus
7	M	55 years	No	Wood piece	Right lower lobe
8	M	24 years	No	Piece of dental filling	Left lower lobe

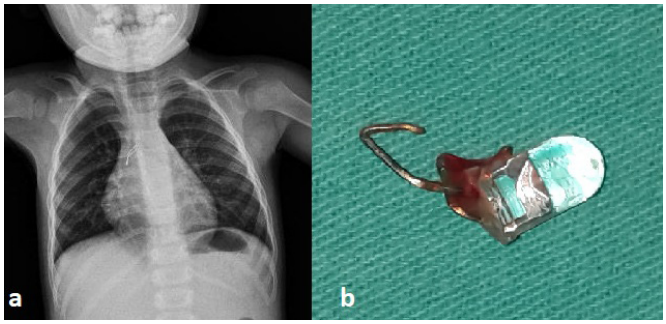

Figure 5. (a) Foreign body with the appearance of 2 wires in PA chest x-ray, **(b)** removed LED of remote control.

In delayed cases, although a bronchoscopy was performed for the etiology of recurrent infection and bronchiectasis, no endobronchial lesion was observed, and a foreign body was detected in the resection material. In one case, after the consolidation in the right lower lobe was removed by wedge resection, a hard body was detected during palpation of the parenchyma and a piece of wood was seen endobronchially (Figure 6, Table 2).

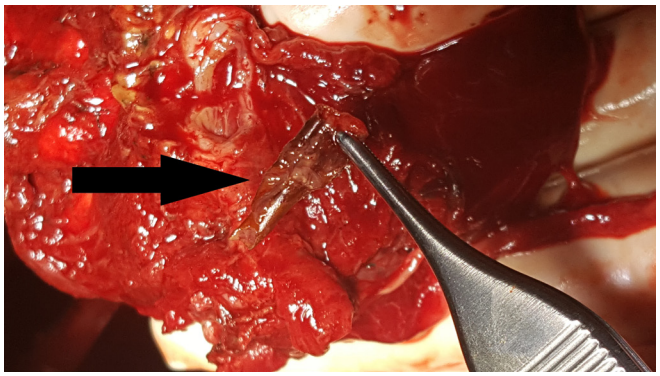

Figure 6. Wood piece detected in lung parenchyma and removed by wedge resection.

In one case who had permanent tracheostomy due to laryngectomy, the spoon handle that was aspirated during secretion cleaning was removed from the tracheostomy by bronchoscopy under local anesthesia (Figure 7).

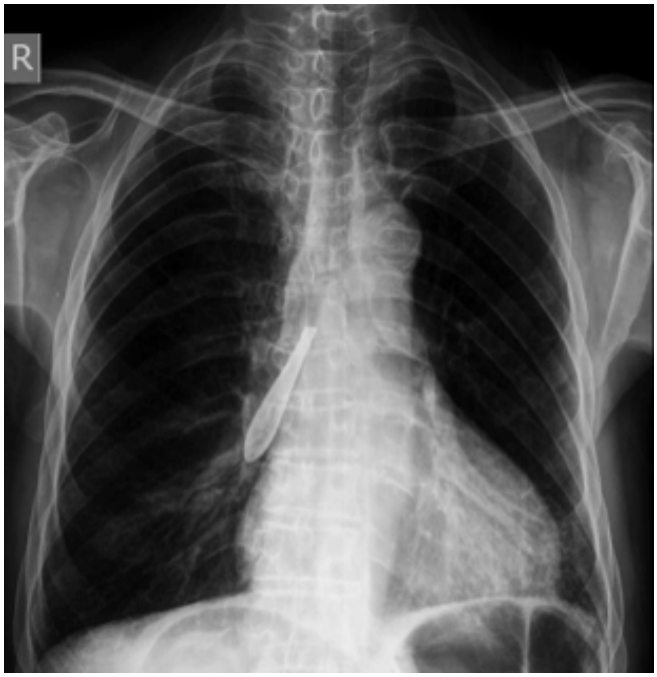

Figure 7. Metal spoon handle in the right main bronchus.

Discussion

Tracheobronchial foreign body aspirations can be seen at any age, however most frequently are encountered in the age group of 1-3 [6]. The main reasons why foreign body aspirations are common in infants and children are as follows: Individuals in this age group are interested in the objects around them; they tend to put foreign objects into their mouths for the purpose of recognition; they lack molar teeth; their chewing functions are insufficient; and they can aspirate food in the mouth while crying and shouting, while the neuromuscular structures related to the protection of the airways are not sufficiently developed [6]. For this reason, infants and children can aspirate novel foreign objects that are of interest in our study, such as stones and LED lamps, while trying to "understand" them with their mouths.

Table 2. The findings of physical examination, the time of diagnosis and the treatment.

Patients	Clinical findings	Time of diagnosis	Anesthesia	Treatment
1	No pathologic respiratory sound	0-8 hours	General	Bronchoscopy
2	Rhonchus bilaterally	0-8 hours	General	Bronchoscopy
3	No pathologic respiratory sound	0-8 hours	General	Bronchoscopy
4	Rhonchus at right hemithorax	8-16 hours	General	Bronchoscopy
5	Stridor	0-8 hours	General	Bronchoscopy
6	No pathologic respiratory sound	0-8 hours	Local	Bronchoscopy
7	Fever, cough, sputum	6 years	General	VATS, wedge resection
8	Cough, No pathological respiratory sound.	1 year	General	Lobectomy

Patients often present with acute respiratory distress and cough. Cough is caused by movement, irritation, and edema of the foreign body in the bronchus. After the foreign body has settled in the bronchi, the cough decreases and, depending on its localization, dyspnea often occurs [4-8].

Radiological evaluation should be performed in all cases in which a tracheobronchial foreign body is suspected; the diagnosis should be ruled out in individuals with normal radiology [9]. The nature of the aspirated foreign body affects the clinic. Tracheobronchial foreign bodies are often localized to the right bronchial system due to the anatomical angle. The right main bronchus is a continuation of the trachea, and is shorter and wider than the left. The dimensions of the angles in children are close to those in adults. In this study, four of the foreign bodies were seen in the right main bronchial system and two in the left bronchial system. No foreign body was detected in the carina. An interesting situation in another case was the pediatric patient who had emphysema on the right due to near right total bronchial obliteration, but who was initially diagnosed with asthma and was followed clinically for one year under this diagnosis. These rare occurrences show the importance of anamnesis and radiology in patients with a suspected foreign body.

Rigid bronchoscopy is a preferred method in children [5,6]. Thanks to its wide canal structure and lumen, the lung is easily ventilated by the anesthetist and bronchoscope also allows access to the foreign body [10]. Research suggests using steroids before and after bronchoscopy to reduce the incidence of postoperative subglottic edema that will require urgent tracheostomy [5-11]. For this reason, steroid treatment was started before bronchoscopy and continued for 24 hours at a dose of 1 mg/kg. During foreign body removal in foreign body aspiration cases, larynx edema, pneumomediastinum, pneumothorax, bleeding, and cardiac arrest can be seen [10-13].

Foreign body aspirations are rarely seen in adult patients. High-risk cases include the elderly, alcohol addicts, those with convulsions, users of sedative or hypnotic drugs, and people with neuromuscular disease, mental retardation, or dental prosthesis interventions [14,15]. In this study, one of the adult patients aspirated the foreign body through the permanent tracheostomy.

Late-diagnosed foreign body aspirations can be clinically present with lung and pleural complications. Complications can vary due to the localization of the foreign body, its type, and the time until diagnosis. Prolonged fever, hemoptysis, chronic cough, recurrent lung infections, bronchiectasis, bronchial stenosis, and lung abscess are some of the possible complications [16]. When irreversible conditions such as bronchiectasis or pulmonary abscess occur, lung resection is required [17,18]. Generally, lower lobes are affected and postoperative histopathological results show a foreign body in the lobar bronchus [19].

In conclusion, tracheobronchial foreign body aspirations are important causes of morbidity and mortality in childhood. Cases that are not noticed in the early period may present later with lung abscess, bronchiectasis, or bronchopneumonia. It should also be kept in mind that clinicians can encounter foreign bodies that are composed of both metallic and plastic components, or unusual foreign bodies that present with pneumonia, which require long diagnosis and treatment periods. Anamnesis and physical examination findings correlated with anamnesis are more important than the other examinations in pediatric populations. We recommend that endoscopic examinations be performed in every suspicious case and that if an unusual foreign body is detected, surgeons should use novel body removal methods and maneuvers besides conventional foreign body removal techniques before switching to the thoracotomy.

Declaration of conflicting interests

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Case Report

Atypical uniportal thoracoscopic resection of a giant thymolipoma

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ABSTRACT

Thymolipoma is a rare, slow-growing, benign anterior mediastinal tumor consisting of mature adipose tissue and thymic tissue. Herein we describe the case of a completely excised giant thymolipoma with uniportal video-assisted thoracoscopic surgery, which was detected incidentally on chest X-ray, with the review of the literature. A 30-year-old male patient was hospitalized to the department of general surgery with the diagnosis of appendicitis. Preoperative chest x-ray revealed mediastinal enlargement extending to the diaphragm at right paracardiac area where cardiac contours were erased and cardiomegaly-like appearance was observed. In the contrast-enhanced computed tomography of the chest, a massive mass of soft tissue was detected in fat density. The mediastinal lesion was completely excised with uniportal VATS. Histopathologically, the tumor was reported to be thymolipoma. Thymolipoma it should be totally removed with VATS surgery for both diagnosis and treatment.

Keywords: thymolipoma, uniportal VATS, mediastinal mass, giant

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Introduction

TThymolipoma is an uncommon benign tumor of the thymus consisting of thymic tissue and mature fatty tissue. It accounts for 2-9% of all tumors originating from thymus [1,2]. It was first described by Lange in 1916 and the term was used for the first time in the literature by Hall in 1949 [1,3].

Thymolipoma may be identified incidentally during a diagnostic screening for other medical problems and may grow large dimensions and manifest themselves clinically by signs of compression on adjacent structures such as shortness of breath, cough, palpitations, hypotension, tachypnea, the fullness of the neck veins and edema in the lower extremities [4].

It can be seen at any age, but it is most common in children and in young ages. It is difficult to distinguish radiologically from other mediastinal masses, however, hyperplasic thymus and adipose tissue-like density may be determinative in contrast-enhanced computed tomography of the chest. We describe the case of a completely excised giant thymolipoma via uniportal video-assisted thoracoscopic surgery (VATS) which was detected incidentally on chest X-ray, with the review of the literature.

Case Report

A 30-year-old male patient was hospitalized to the department of general surgery with the diagnosis of appendicitis. On preoperative chest X-ray, cardiomegaly-like appearance and mediastinal enlargement extending to the diaphragm were observed in the right paracardiac region and the contours of the right heart were erased (Figure 1).

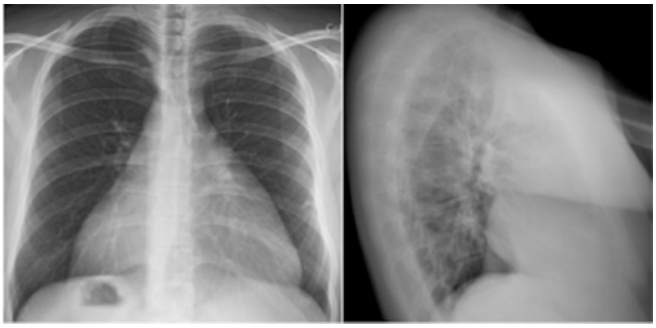

Figure 1. Preoperative chest X-ray.

After being healed from the emergency situation, a contrast-enhanced computed tomography of chest (CCT) was taken under elective conditions. A massive soft tissue mass of fat density and giant size was observed, which completely filled the anterior mediastinum, extending from the right paracardiac area to the diaphragm, with clear borders with the mediastinal structures, not disrupting the contour of the mediastinal tissues (lesion dimension; 213x65 mm) (Figure 2).

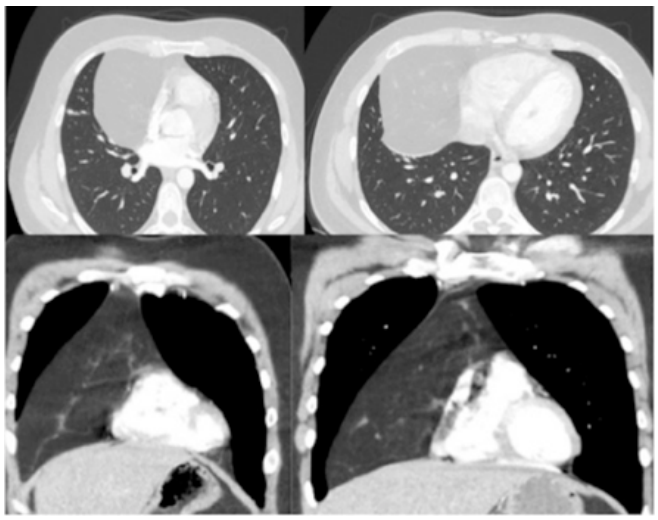

Figure 2. Preoperative contrast-enhanced computed tomography.

Although there was no additional disease in his medical history, when his anamnesis was deepened, it was found that there was shortness of breath and fatigue those had existed for a while and came with effort, were observed. Results of other clinical laboratory tests were normal. Biopsy and additional radiological examination were not performed in this case, because the patient was considered to have benign anterior mediastinal mass lesion and surgery was planned for complete excision. After the preoperative preparations were completed, the patient underwent left selective intubation, with a double-lumen endotracheal tube and the hemithorax was explored via uniportal VATS (3 cm incision) approach incision through the right fourth intercostal space on anterior axillary line. The mediastinal pleura was dissected and an encapsulated lesion of benign character was observed. After the thymic vein was clipped from the superior mediastinum, the left side mediastinal pleura was also opened (Figure 3).

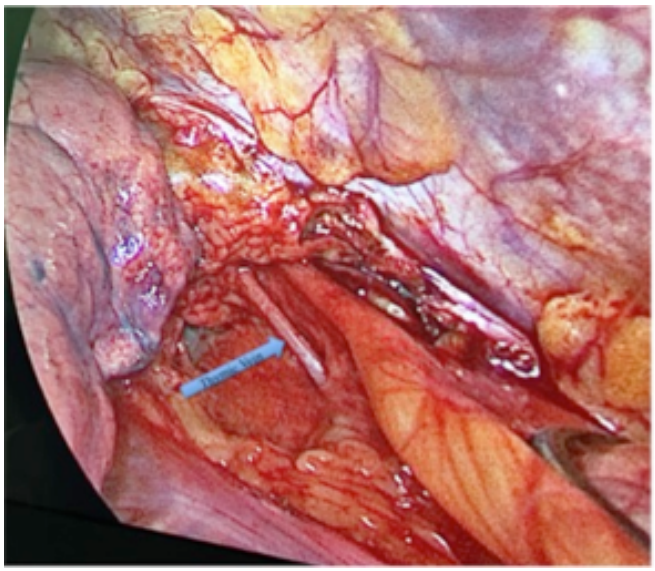

Figure 3. Intraoperative anterior mediastinum and thymic vein image.

The capsule was preserved and the lesion was dissected from the pericardial and diaphragmatic surfaces with the help of electrocautery. At this point, the best effort was taken to preserve the phrenic nerve from an unintentional injury. The lesion could not be removed in one piece because of its giant size, was extracted with two separate endobags in two pieces, by dividing it into two in the endobag while maintaining the safe oncological principles (Figure 4).

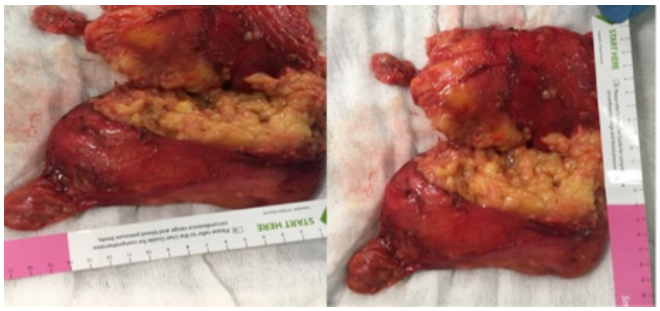

Figure 4. Giant thymolipoma total excision two pieces.

The incision was lengthened by 1 cm for lesion removal. Assistance was received from endoscopic and conventional surgical instruments that we constantly use in uniportal VATS application

Tube thoracostomy was performed from the same incision and no postoperative complication was observed in this case. On the second postoperative day, the chest tube was removed and on the third day, he was discharged after an uneventful course (Figure 5).

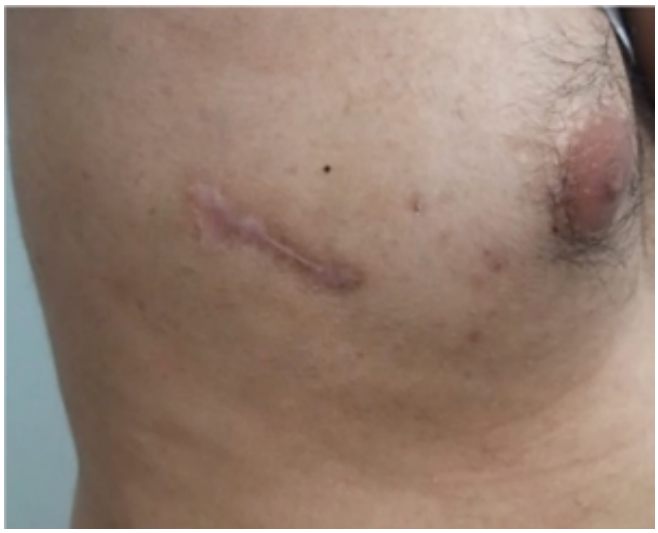

Figure 5. Uniportal VATS incision scar.

On macroscopic examination of the specimen, encapsulated two masses weighing totally 666 g, with the size of 16.5x11x3.5 cm and 13x10.5x3.5 cm were detected. The cut surface of the masses was solid and yellow-colored. Histopathologically, the tumor was reported to be thymolipoma. It was characterized by mature adipose tissue surrounded by a thin fibrous capsule and admixed with strands of atrophic thymic tissue containing Hassall corpuscles and calcification in some areas (Figure 6). The patient has been followed up for 10 months without any problem.

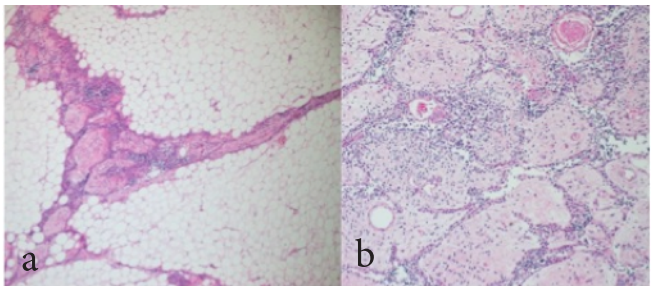

Figure 6. (a) Mature adipocytes admixed with atrophic thymic tissue (HE, 40X), **(b)** a closer view demonstrating Hassall corpuscles (HE, 100X).

Written informed consent was obtained from the patient for publication of his data.

Discussion

Thymolipomas are characterized by mature adipose tissue. It is a slow-growing, encapsulated tumor of both

mesodermal (fat) and endodermal (thymus) origin. Different from thymoma, it doesn't show mitosis and atypia, mature adipose tissue can be clearly separated from thymus tissue, the surrounding tissues usually don't show invasion and malignant behaviour, such as distant metastasis. These tumors appear especially in the 3rd and 4th decades and are mostly asymptomatic. However, they can rarely grow to huge dimensions and be symptomatic. In our case tumor was detected incidentally in the 3rd decade and although the lesion enlarged to giant dimensions, it didn't cause serious symptoms. In some studies, cases of thymolipoma with progressive huge dimensions; it has been reported that there were symptoms of dyspnea, chest pain, cough and respiratory infections [4,5]. In the differential diagnosis of anterior mediastinal lesions, the most effective method in radiological evaluation is contrast-enhanced CCT [6,7]. There are several publications in which CCT is inadequate and MRI has advantages in cases where the borders of mediastinal structures cannot be clearly separated and benign-malignant distinction cannot be made clearly [8,9]. In our case, CCT was observed sufficient in differential diagnosis and additional radiological examination was not required.

The surgical approach preferred in mediastinal lesions growing huge dimensions is sternotomy and thoracotomy [2,10]. Thoracoscopic surgery has not been recommended due to the inability to remove these giant size lesions completely, the spread of tumor cells to the pleura and the risk of recurrence and VATS applicability has been reported only in small size lesions [10,11]. Uniportal VATS is a commonly used surgical approach in our clinic for mediastinal lesions. This surgery was completed with right uniportal VATS because it was considered as a benign and encapsulated lesion. Since the lesion was too large to be extracted with a single endobag, the giant lesion dissected from all mediastinal structures was divided into two parts in the endobag and completely extracted with two separate endobags.

Radiologically, lipoma, liposarcoma, teratoma, cardiomegaly, pericardial fat pad, pericardial effusion, pericardial tumors, congenital diaphragm hernias should be considered in the differential diagnosis. Making the correct diagnosis for thymolipoma by fine-needle aspiration cytology is not always possible, because the cytological material should contain both thymic and lipomatous components for differential diagnosis with other lipomatous tumors. In our opinion, it is not very satisfactory to perform needle biopsy to such type of lesions for diagnosis. In our case the differential diagnosis and the type of surgical approach were considered via CCT so that a preoperative biopsy was not indicated. Both definitive diagnosis and treatment were achieved with complete surgical resection.

Although the thymolipoma grows to huge dimensions, it may not show any symptoms and progress without symptoms. Mostly heavier than 500 g when diagnosed. In our case was asymptomatic and weighed 666 g.

As a conclusion, although thymolipoma is a rare benign lesion with no malignant features and no recurrence, it can grow to giant sizes and cause compression signs and symptoms. Therefore, complete excision should be performed with surgery for diagnosis and treatment. It should be kept in mind by experienced clinics that VATS is a good choice of approach, particularly in cases considered to be benign, even in the tumors grown to huge sizes.

Declaration of conflicting interests

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Case Report

A mass-forming extramedullary hematopoiesis case mimicking mediastinal neoplasia

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ABSTRACT

Extramedullary hematopoiesis (EMH) is a condition that usually coexists with hematological disorders and rarely causes mass formation. It can occur anywhere in the body, but very rarely becomes a tumor-like mass in the posterior mediastinum and paravertebral region. A 41-year-old female patient presented with respiratory distress. Radiologically, multiple large mass lesions were detected in the posterior mediastinum, localized bilaterally at paravertebral regions. Diagnostic studies with transthoracic biopsy specimen were showed that the mass lesion was consisting of myelocytes, lymphocytes, erythrocytes and megakaryocytes, so the case was reported as EMH. The case was presented to make a differential diagnosis, because it mimics solid neoplasms at unusual localizations, and may accompany hematological disorders.

Keywords: extramedullary hematopoiesis, solid mass, posterior mediastinum

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Introduction

Extramedullary hematopoiesis (EMH) is the body's compensatory response by the bone marrow to erythropoiesis deficiency, or accelerated destruction of erythrocytes, and refers to a deposit of erythroid precursors in other sites more than the bone marrow and peripheral blood. Although it is seen mostly microscopically deposited in various tissues rarely manifests as hepatosplenomegaly or lymphadenopathy [1,2]. It is usually diagnosed incidentally and, presents rarely as a posterior mediastinal mass, mimicking any kind of a mediastinal tumor. Intrathoracic EMH is a rare pathology and only very few case reports have been described in patients with chronic myeloproliferative disorders, especially myelofibrosis with myeloid metaplasia, anemia, thalassemia-sickle-cell anemia, MYH9-related thrombocytopenia, polycythemia and spherocytic anemias [1-9]. The patients with EMH, are most commonly asymptomatic or have symptoms related to anemia such as fatigue and dizziness. Rarely, they occur as a solid mass and the patients have mass related symptoms [10,11]. The posterior mediastinum is an uncommon localization for EMH, except some sporadically reported intrathoracic manifestations. In radiological screening with computed tomography (CT) and/or Magnetic Resonance Imaging (MRI), it is usually identified as bilateral, multiple, and well-circumscribed mass with soft tissue density [12,13].

The case was reported to avoid misdiagnosis and unnecessary surgery, due to the unusual location of EMH, by mimicking solid neoplasm in the posterior mediastinum as an unusual location. Besides, it was reported to raise awareness of hematological neoplasms that manifest themselves with anemia and form mass lesions.

Case Report

A 41-year-old woman admitted to the hospital with dyspnea. Her physical examination was normal and the laboratory studies revealed mild anemia (Hgb: 9.4 g/dL, RBC: 3.37 x 10^{12}/L, CT: 33.2 %, MCV: 98.5 fL). Abdominal ultrasonography and CT revealed the spleen enlargement with a size of 14 mm in largest axis and 149x91x143 mm respectively. In positron emission tomography (PET)- CT, hematopoietic system activation was detected in spleen and bone marrow. Thorax CT showed a 109x95x64 mm mass lesion lying posteriorly between 6 to 10th thoracic vertebrae at the right side. A second paravertebrally localized lesion was on the left side, sized as 61x47x29 mm, at the level of thoracic 8-10th vertebrae, and a third 24x13x9 mm sized mass lesion at the level of the left costovertebral junction, close to the thoracic 7-8th vertebrae, adjacent to pleura. Mediastinal lymphadenopathies were detected at right paratracheal and left prevascular regions with 11 mm of the largest (Figure 1).

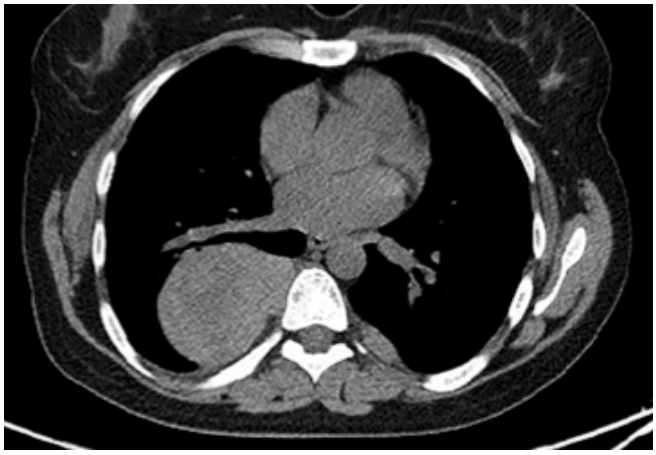

Figure 1. Computed tomography of the thorax demonstrating sharply demarcated bilateral prevertebral-paraspinal masses of soft tissue density. Pulmonary parenchyma and bone structures were normal.

A tru-cut biopsy was performed from the mass that was located in the posterior mediastinum. Microscopically, the composition of cells were lymphocytes, erythrocytes, plasma cells, megakaryocytes and histiocytes (Figures 2a and b) where the structure showed similarity to bone marrow.

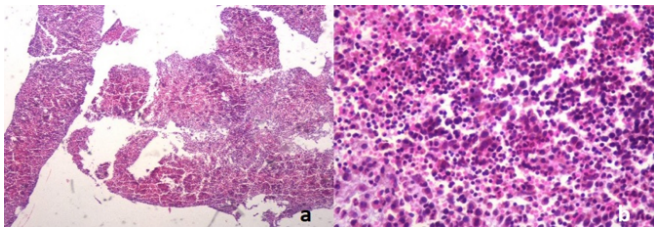

Figure 2. (a) Normal hematopoietic tissue fragments observed in light microscopy at the smallest magnification field (HEX40), **(b)** a normal hematopoietic tissue without dysplasia, which is composed of blood cell precursors, reminiscent of bone marrow (HEX200).

Immunohistochemical stains showed that some lymphocytes were focally stained with CD3, the other lymphocytes were stained with CD20. Megakaryocytes were

positive with CD61 (Figure 3a), myelocytes were positive with MPO (Figure 3b). Erythrocyte precursor cells were found to be positive with GLCO A (Figure 3c) and monocytes were positive with CD68 (Figure 3d).

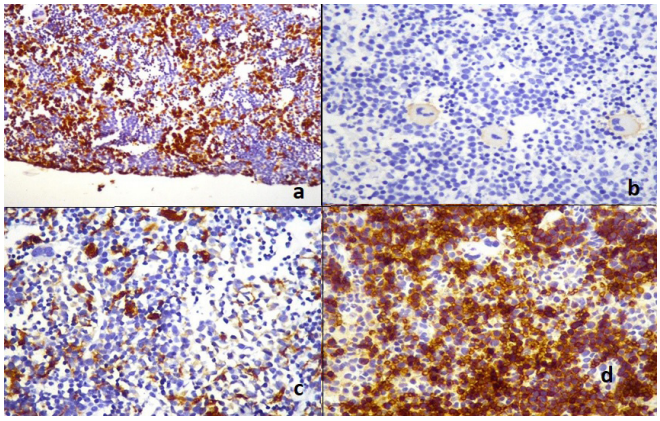

Figure 3. (a) Staining of myeloid serial cells in EMH tissue with myeloperoxidase (IHC, X40), **(b)** staining of megakaryocytes in EMH tissue with CD 61 (IHC, X100), **(c)** staining in histiocytes with CD 68 (IHC, X100), **(d)** staining in erythrocyte precursor cells with Glycophorin A (IHC, X200).

The cells showed negative immunoreactivity with pancytokeratin, CD34 and CD117. In light of the whole clinical and histological features, this case was diagnosed as extramedullary hematopoiesis. With the final diagnosis, the patient referred to hematology clinic and blood transfusions with symptomatic management were applied. In her 10-months follow up period the whole process was uneventful.

Written informed consent was obtained from the patient for publication of her data.

Discussion

The source of normal hematopoiesis is bone marrow. In particular, the lower skull, vertebrae, shoulder and pelvic girdles, ribs and bone marrow located in the sternum have this function. The hematopoietic active bone marrow continues to its function until late adolescence. EMH is considered as a compensatory mechanism that occurs secondary to inadequate bone marrow function [2]. The exact pathogenesis of EMH is unclear, transforming of embryonal rests of osteogenic tissue may be accused. Besides, it may originate from the extension of hyperplastic bone marrow through the ribs and vertebral bodies. Some lesions are silent and waiting to be discovered by chance. Rare ones have signs of compressing neighboring organs [11,14,15]. EMH may rarely occur in unexpected places and as a lesion mimicking a tumor, forming a mass. For this reason, it is often misdiagnosed [2,8]. As in our case, the posterior mediastinum is among these rare places [2].

The causes of EMH may be pathological or physiological. There are wide varieties of pathologic conditions in which disturbance of the normal blood-forming marrow may be associated with the formation of extramedullary hematopoietic tissue. Common causes of EMH include spherocytic anemia, erythroblastosis of newborn, thalassemia, pernicious anemia in the period of relapse, macrocytic anemia of hepatic origin, carcinomas with bone marrow invasion, Hodgkin's disease, lymphoma, leukemia, osteosclerosis and myeloproliferative syndrome [1-8].

The mechanism of origin of these extramedullary foci is unknown, but there are several theories like embolization, direct extension, myelostimulation or redirected differentiation, which explain the pathogenesis of EMH, but none of them is widely acceptable [15]. EMH is a physiologic compensatory mechanism that is usually associated with hematologic disorders as in our case and most of the other reported cases. EMH cases without hematological disorder have also been described [10].

Symptoms related to mass formation seen in EMH cases are related to the location of the lesion [2,10]. Patients may sometimes be asymptomatic [2,11]. Although the masses those are locating in the posterior mediastinum usually cause no symptoms, the ones with large dimensions might cause respiratory problems related to compression and neurologic deficits related to the level of involvement. The patients have complaints due to spontaneous pneumothorax, hemithorax and rapidly fatal respiratory failure [10,11,15]. Our case also had severe respiratory distress. Also, anemia was found in the patient who had complaints of weakness and fatigue.

It was determined that the case, which was immediately biopsied with the concern of the possibility of advanced neoplastic lesions, was a case of EMH secondary to anemia, forming a solid mass. A population of cells resembling bone marrow was observed in routine preparations obtained from the biopsy. Mesenchymal originated mediastinal neoplasms, especially lymphomas, were also included in the differential diagnosis. However, those were excluded

by the presence of precursor cells, same as in the bone marrow, which constitutes blood cells examined in light microscopy. Possible lymphoreticular tissue neoplasms were also excluded from the differential diagnosis due to the absence of features such as atypia, pleomorphism, and disorganization, and determination of cell origin by additional immunohistochemical examinations.

Treatment of EMH diagnosed solid masses, can be variable depending on the patient and the disease. These methods are the use of blood transfusion, radiotherapy, surgical decompression, hydroxyurea and JAK2 inhibitors. JAK2 inhibitors and TGF-β ligand traps that improve the erythropoiesis process are being tested in patients with thalassemia and EMH who do not respond to treatment, and the results look promising. In the absence of severe symptoms and complications, EMH treatment may not be required [2]. Our patient whose symptoms started to regress with blood transfusion treatment is followed up by the clinic.

In conclusion, EMH is a rare pathology, but can be serious with mortal complications and also can be confused clinically and radiologically with other benign or malignant lesions in the posterior mediastinum. It should be kept in mind in the differential diagnosis of resistant anemia cases with radiologically determined mass. Clinician-radiologist-pathologist collaboration is required to avoid misdiagnosis.

Declaration of conflicting interests

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Case Report

A rare presentation of a rare disease: endobronchial hamartoma with lobar bronchiectasis

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ABSTRACT

Benign lung tumors are very rare, endobronchial hamartomas -one of which- are even more rare. Endobronchial masses tend to represent themselves via obstruction related symptoms and endobronchial hamartomas are not an exception. It is important to diagnose endobronchial masses before they bring untreatable damage to the lung. It is also important to differentiate endobronchial hamartomas from endobronchial malignancies, such as carcinomas, for they also tend to act mildly symptomatic for a long period of time. In our case, the patient was admitted to our clinic with the symptoms of cough and mild hemoptysis. A computed chest tomography showed total bronchiectasis of right upper lobe along with an endobronchial mass in the right upper lobe bronchus. Bronchoscopic biopsy of the mass revealed no diagnosis. We performed a right upper lobectomy and the pathological examination resulted as endobronchial hamartoma. There are numerous cases about endobronchial hamartomas in the literature which represented with countless symptoms and diseases as persistent cough, recurrent pneumonia, local bronchiectasis and so forth. Our case of endobronchial hamartoma representing with total bronchiectasis of a whole lobe of the lung is the first and only case in the English literature to our knowledge.

Keywords: endobronchial hamartoma, endobronchial mass, bronchiectasis, videothoracoscopic surgery, lobectomy

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Introduction

Although lung tumors are predominantly malignant, benign tumors of lung - despite being rare - are clinically important due to their radiological and/or symptomatic presentation. Endobronchial benign tumors are also uncommon and they represent 2% of all lung tumors [1]. Hamartomas are the most common benign tumors of tracheobronchial tree and the lung [2]. They are mostly seen in the peripheral zones of the lung parenchyma. Endobronchial hamartomas are also rare and tend to locate in large bronchi. It may easily be confused with malignant tumors, such as carcinoid tumors. Having said that, endobronchial hamartomas may also cause irreparable lung damage due to obstruction, thus, diagnosis and treatment in the early stages are of vital importance.

Case Report

A 50-year-old woman was admitted to our clinic for evaluation of persistent cough and mild hemoptysis. A detailed examination of patient's medical history revealed that the onset of the mentioned symptoms was nearly 10 years prior to admittance. According to the patient's statement, symptoms have started rather lightly and improved over the years progressively. Cough was persistent, usually nonproductive and intensified lately. Hemoptysis has started as blood-tinged sputum and increased seldom, if ever as much as full table spoon. Patient has sought medical help from time to time and had already the diagnosis of bronchiectasis from about 5 years ago. Patient has stated that she visited the hospital irregularly and never received any proper treatment per se. Patient has also stated that she never underwent bronchoscopy or get diagnosed with endobronchial mass. There was no other disease history and the patient was a nonsmoker. A computed tomography (CT) was administered in another hospital before she was admitted, and that CT demonstrated a right upper lobe bronchiectasis along with an endobronchial mass of 0.5 cm (Figure 1).

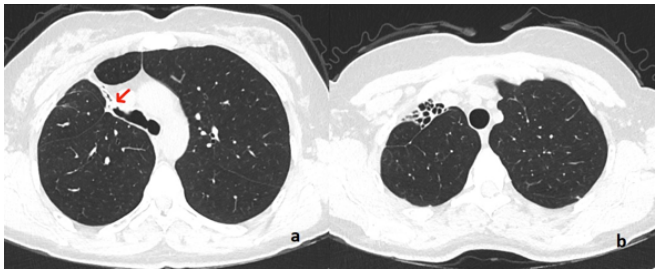

Figure 1. (a) Axial view of computed tomography showing the endobronchial mass (arrow), **(b)** bronchiectasis of the right upper lobe.

A fluorodeoxyglucose positron emission tomography (F-18 FDG PET/CT) was also administered at that hospital and it showed a minimally elevated maximum standard uptake volume (SUVmax) as 1.9. Bronchoscopy was performed in our hospital and the endobronchial mass was visualized as a smooth surfaced polypoid body at the entrance of posterior segmental bronchus of right upper lobe, which narrowed the bronchus of right upper lobe. A bronchoscopic biopsy was performed and its pathological examination reported superficial bronchial mucosa, indicating that the biopsy was taken superficially. We performed a video-thoracoscopic right upper lobectomy, since the video-thoracoscopic exploration revealed a totally shrunk right upper lobe and thinned out vasculature of the same lobe in accordance with preoperative CT scan. Another side note of the operation is that the lower and middle lobes were expanded compensatory to fill right hemithorax. An intraoperative frozen section was performed after the lobectomy and it reported the bronchial margins negative and also the endobronchial nodule was in benign nature (Figure 2).

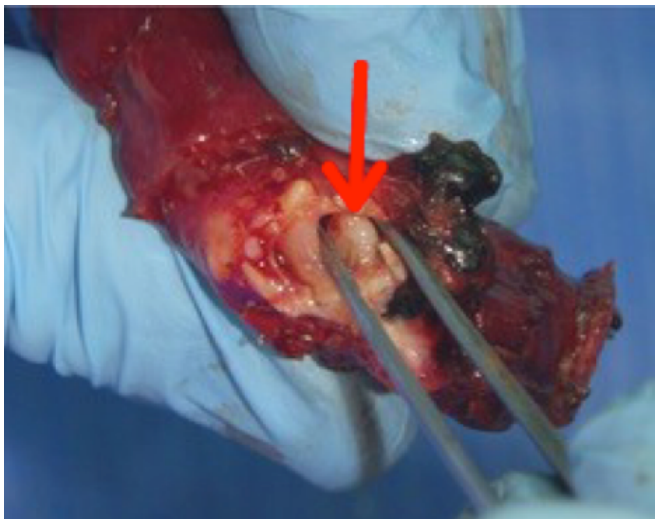

Figure 2. Pathology specimen; arrow points the endobronchial mass.

Histopathological examination of the specimen revealed the nodule as endobronchial hamartoma (Figure 3).

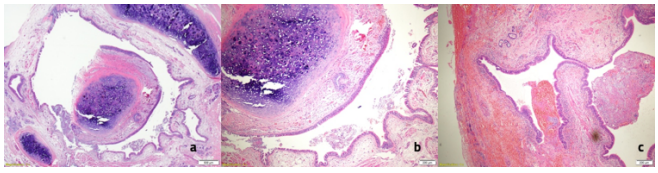

Figure 3. (a) The endobronchial hamartoma structure with mature chondroid tissue is seen inside of the bronchial wall (x4), **(b)** Closer view of the endobronchial hamartoma; the surface is covered by mature bronchial epithelium and chondroid tissue is seen in the center (x20), **(c)** Lung parenchyma with bronchiectatic changes (x20).

Written informed consent was obtained from the patient for publication of her data.

Discussion

Endobronchial hamartomas are predominantly benign tumors and are rare clinical cases. It is important to diagnose endobronchial masses in early stages, before the irreparable lung damage takes place. Obstruction by the endobronchial mass may cause recurrent pneumonia, bronchiectasis, post-obstructive atelectasis, and also malignancies [3].

There are various cases in the literature which represented with recurrent pneumonia, persistent cough and even atrial fibrillation along with countless asymptomatic cases [2,4,5]. Some of these cases were reported to be with local bronchiectasis but there is no lobar bronchiectasis in the literature caused by an endobronchial tumor. Due to its nature, lobar bronchiectasis tends to reveal itself as recurrent pneumonia and frequent hospitalization and/or medication history [6]. In spite of our patient have had lobar bronchiectasis, there was no recurrent hospitalization or history of recurrent pneumonia. Nonetheless our patient showed persistent cough and mild hemoptysis, these symptoms does not necessarily indicate bronchiectasis, let alone lobar bronchiectasis.

Hamartomas, including endobronchial ones, incline to stay below-radar in F-18 FDG PET/CT [7,8]. Initial examination and evaluation of all findings, including CT scan and SUVmax value, directed the route towards low activity nodules of the lung: Typical carcinoid, pulmonary adenoma, bronchioloalveolar carcinoma and of course, endobronchial hamartoma [9-11]. There are many options in terms of treatment for endobronchial lesions. Bronchoscopic treatment may be the first one to think as a safe choice: diode laser or argon plasma coagulation and cryotherapy [12]. We have steered for an anatomical resection after a non-diagnostic bronchoscopic biopsy attempt, due to the localization of the mass and bronchiectatic appearance of the right upper lobe in preoperative CT scan. A bronchotomy also comes to mind, but the localization of the mass prevented the idea and also an anatomical resection was already inevitable due to bronchiectasis.

In conclusion endobronchial tumors may cause a variety of symptoms and problems. It is important to detect such masses in early stages, before the irreparable damage takes place. Bronchiectasis, as an irreversible damage entity of the lung, may be the outcome of endobronchial tumors. Our case showed that endobronchial hamartoma caused a total lobar bronchiectasis and is the sole case in the English literature to our knowledge.

Declaration of conflicting interests

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Case Report

Cryosurgery of endobronchial tuberculosis facilitated by Foley's catheter usage for both intubation and distal airway safety

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ABSTRACT

A 35-year-old female with a reproductive cough, dyspnea, stridor, and intermittent hemoptysis was evaluated by fiberoptic bronchoscopy (FOB). An endobronchial lesion was observed 2 cm distal to the vocal cords, occluding two-thirds of the tracheal lumen. Rigid bronchoscopy and total excision of the lesion with cryosurgery were planned. Under general anesthesia, a 14-mm rigid bronchoscope (RB) was introduced. As a facilitative new technique, the patient was intubated with an 18F Foley catheter, which was introduced close to the RB. The cuff of the catheter was then inflated distally to the lesion. Subsequently, the catheter was connected to a mechanical ventilator to ensure the safety of the airway while preventing hypoxia. Total excision of the mass was performed via cryosurgery. Immediately after, the catheter balloon was deflated, and a fiberoptic bronchoscope was introduced through the RB to explore the distal bronchial system for aspirated tissue fragments and secretions. With this facilitative approach, the distal airway was kept clean of secretions and tissue fragments. The final pathology of the mass was granulomatous inflammation and necrosis, and the patient was referred to a tuberculosis clinic for medical treatment.

Keywords: dyspnea, endobronchial tuberculosis, endobrochial treatment, cryosurgery

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Introduction

Interventional bronchoscopy procedures, used by both interventional pulmonologists and thoracic surgeons, have a high success rate, with low morbidity and mortality. Rigid bronchoscopy with cryosurgery and/or argon plasma coagulation is the most common treatment method for endobronchial occlusive lesions [1]. Most of these lesions are liable to bleed, and the bronchial tree distal to the lesion may occlude with blood cloths, which can lead to hypoxia. The development of hypoxia during the procedure complicates this already challenging intervention. There are specific suction catheters and thin lumen intubation tubes designed for use in rigid bronchoscopy procedures [2].

In this case report, we used a simple Foley's catheter for intubation as a facilitative technique to provide distal airway safety while avoiding hypoxia in cryosurgery of the large endotracheal lesion.

Case Report

A 35-year-old woman was admitted to our clinic with a reproductive cough, night sweats, weight loss, mild intermittent hemoptysis, weakness, and progressive dyspnea and stridor. The patient was first admitted to hospital 3 months earlier. Since then, she had been misdiagnosed with asthma and received medical treatment. In the patient's family history, her mother and aunt were both received medical treatment for pulmonary tuberculosis. The patient was admitted to an otolaryngologist, and fiber laryngoscopy performed by him revealed an endotracheal mass 1.5 cm in size distal to the vocal cords. Neck computed tomography revealed a 12 × 10 × 12 mm polypoid soft tissue mass with lobulated margins on the posterolateral wall of the trachea (Figure 1).

Thorax tomography revealed nothing else of note, with no suspicious parenchymal lesions. Three sputum samples obtained on three consecutive days were negative for acid-fast bacillus (AFB) staining. Fiberoptic bronchoscopy was then performed and revealed a mass prone to bleeding 2 cm below the vocal cords. The tracheal lumen hardly allowed the FOB to pass distal to the lesion. There were no other abnormal findings in the tracheobronchial tree. The macroscopic findings suggested a benign tracheal lesion. A biopsy was not performed to avoid bleeding. A bronchoalveolar lavage sample was also negative for AFB staining. Rigid bronchoscopy and cryosurgery were planned.

Under general anesthesia, a 14-mm RB was introduced. A polypoid lesion occluding nearly three-quarters of the tracheal lumen, originating from the right anterolateral tracheal wall was observed 2 cm distal to the vocal cords. We had to urgently secure the airway, as the lesion was bleeding profusely during the exploration with the RB. To secure the distal airway from blood and to maintain ventilation, the patient was intubated with an 18F Foley catheter under guidance of the RB. The catheter was introduced through the vocal cords adjacent to the RB (Figure 2).

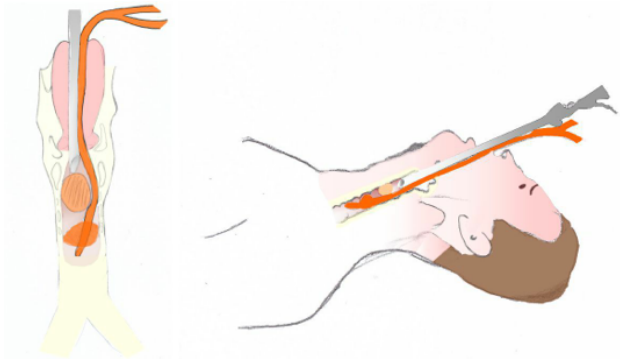

Figure 2. Illustration showing the intubation of the patient by a Foley's catheter introduced adjacent to the rigid bronchoscope.

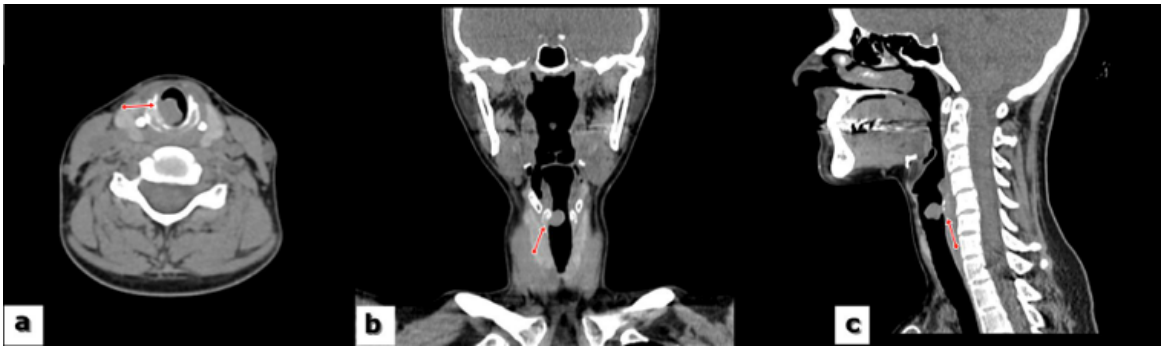

Figure 1. Neck CT scan showing polypoid, soft tissue mass distal to the vocal cords.

The cuff of the catheter was then inflated distally to the lesion. The tip of the catheter was connected to a mechanical ventilator. The luminal diameter of the 18F catheter allowed a standard mechanical ventilator to the used. As the blood gas analysis was within normal ranges, jet ventilation was not required. Total mass excision and homeostasis were undertaken by cryosurgery. **Video-1.** Cryosurgery of an endotracheal mass through rigid bronchoscope accompanied by the usage of a Foley's catheter as an intubation tube. http://cts.tgcd.org.tr/submit/pdf-files/in/532-CTS-532-8-video.mp4

The procedure was completed without any complications. The final pathology of the mass was granulomatous inflammation and necrosis. The patient was referred to the tuberculosis clinic for further medical treatment.

Written informed consent was obtained from the patient for publication of her data.

Discussion

In this case report, we described the use of Foley's catheter as an effective way to facilitate the treatment of an undiagnosed semiocclusive endotracheal lesion with cryosurgery. Endobronchial tuberculosis (EBTB), which is a serious complication of pulmonary tuberculosis, has been reported in 10-40% of patients with active pulmonary tuberculosis [3,4]. These cases are often misdiagnosed as bronchial asthma or lung cancer [4]. Some patients with EBTB may have normal radiological findings (10–20%), and this may lead to a delay in the diagnosis [5]. Our patient was misdiagnosed with asthma and received medical therapy.

The clinical features of EBTB are variable, and symptoms such as anorexia, weight loss, and night sweats might not be present in some cases. A progressive cough unresponsive to antitussive treatment is the most common presentation of EBTB. Sputum production is rare. Hemoptysis may occur, but it is rarely massive [6]. Computed tomography is a valuable diagnostic tool to differentiate EBTB from other bronchial lesions, such as bronchial stenosis and obstructions. A bronchoscopic examination is also important in the differential diagnosis to exclude other possible causes of EBTB-like symptoms [7,8].

EBTB may lead to serious complications, such as severe bronchostenosis, resistant tuberculosis, recurrent pulmonary infections, atelectasis, and bronchiectasis. It may even result in death due to respiratory failure and asphyxia [9,10]. Early diagnosis and antituberculosis treatment before involvement of the deeper airways are important to avoid sequelae of bronchostenosis [5].

Five potential mechanisms believed to be responsible for the development of EBTB are direct invasion from an adjacent parenchymal focus, implantation of organisms from infected sputum, hematogenous spread, erosion of a lymph node inside a bronchus, and lymphatic drainage from the parenchyma toward the peribronchial region [11]. In the present case, there was no parenchymal focus or an adjacent enlarged lymph node, and AFB staining of the sputum was negative.

EBTB is classified into seven subtypes according to its bronchoscopic findings: actively caseating, edema-hyperemic, fibrostenotic, tumor, granular, ulcerative, and nonspecific bronchic. Edematous-hyperemic, fibrostenotic, and tumorous subtypes tend to progress to eventual bronchial stenosis/obstruction within 3 months, despite appropriate treatment [12]. With these EBTB subtypes; sputum cultures, bronchial wash fluid, and biopsy samples typically show positive AFB staining or culturing results. The lesion in our case was similar to tumor-type EBTB. However, it differed from classical tumor-type EBTB because caseous material, usually seen in this type, was not observed [11].

We had no histopathologic diagnose of the endobronchial lesion at the time of the intervention. Noninvasive diagnostic techniques had not poined a current diagnosis. Although the patient had undergone medical treatment for a long time, her complaints had not regressed. The patient in the present case was a breast-feeding mother and had a low quality of life due to her ongoing bronchial symptoms. We did not perform FOB biopsy because of the risk of massive bleeding. Instead, cryosurgery was undertaken for both the diagnosis and treatment of the semiocclusive endotracheal tumoral lesion.

Cryosurgery can be used both in the diagnosis, debulking, and total excision of endobronchial lesions. As cryosurgery is minimally invasive and uses extreme

cold to destroy lesions/tissue, and does not show any activity on cartilage; there is no risk of tissue damage or perforation. In addition, as cryosurgery has no risk of deflagration, the oxygen usage during the procedure is allowed freely. However, there are some risks of the application. Fragments separated from the mass and blood may move distal of the lesion and lead to airway obstruction and hypoxia. To prevent such complications, repeat aspiration of the distal airways is essential [13].

In our case, the location of the lesion just below the vocal cords caused difficulty in ventilation during rigid bronchoscopy. Such difficulty poses a potential medical emergency in the form of hypoxia. To prevent hypoxia, we had to secure the distal airway while maintaining ventilation. With this aim in mind, we used a soft Foley catheter for intubation. It was introduced adjacent to the RB. The balloon of the catheter was inflated distal to the lesion. The proximal tip of the catheter was then connected to a mechanical ventilator. In this way, we not only secured the distal airway but also enabled ventilation through the channel of the catheter. We also created a comfortable viewing and working space through the RB. The total operation time was 25 min. During the procedure, arterial blood gases analysis was conducted approximately every 10 min, and the highest levels of carbon dioxide and lowest levels of oxygen pressure were 55 mmHg and 100 mmHg, respectively.

In conclusion, endobronchial cryosurgery is a well-known treatment method for endobronchial occlusive lesions. The most challenging part of the intervention is securing the distal airway without causing hypoxia. With this in mind, in our case, we used a simple but facilitative technique comprising Foley's catheter intubation close to a RB. To our knowledge, this method has not been reported elsewhere in the literature. We suggest that this new and simple method may be used to ensure the safety of the distal airways in endobronchial interventions and to achieve a comfortable viewing and working space through the RB in selected patients.

Declaration of conflicting interests

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