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Turkish Thoracic Journal
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b. Articles and reviews should be prepared in accordance with the instructions below:

The first page should include the title of the article in English (should not exceed 90 characters) and the running title in English (should not exceed 45 characters).

The second page should include English abstract that do not exceed 250 words. A structured abstract with Objectives, Material and Methods, Results, and Conclusion sections should contain the aim of the study, main results of the study, and a brief conclusion. The above mentioned structure does not apply to the case reports and reviews; a short abstract of no more than 200 words is required.

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In review articles, subtitles should be used in order to provide a better understanding on the subject. In a review article, it would be beneficial to provide different sections such as the context of the problem, historical information, basic knowledge, methodology, animal and human experiments, discussion, conclusion, suggestions and future studies.

Research articles should include separate sections for Introduction, Material and Methods, Results, Discussion. Pharmaceutical products can be mentioned either with their generic or commercial names (generic names are preferred). Commercial names should be written with capital letters, followed by the company and its city in parenthesis. Acknowledgements, references, tables and figure legends should follow the main text. Tables should be presented at the end of the text and each on a separate page.

c. The "Acknowledgements" section should be placed at the end of the text before the references and should not exceed one paragraph.

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f. Figures: All figures should be high-quality (at least 300 dpi resolutions) in .jpeg or .jpg format, and should be provided in black and white. If providing a better understanding of the topic, colored figures will be accepted in limited number. For each manuscript, six figures at most will be accepted. Figures should be numbered with Arabic numeral(s) in order of appearance in the text. The type of the dye that was used, magnification scales, and internal scale bar should be stated for microscopic photographs. A centimetric template should be added for pathologic specimens. Ethical values should be protected in any patient-related photograph or graphs. If the identity of the patient can be revealed by the provided photographs and graphs, a written consent should be requested from the patient. The figures should be cited in parenthesis with their respective numbers within the main text. All figure legends should be on a separate page after references and tables. A written permission is required for reproduced figures.

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i. In puzzling case reports, a short introduction should be followed by the description of the problem, presentation of clue photos and figures, definite diagnosis, and a discussion section where the diagnosis is discussed and educational messages are emphasized.

j. Disagreement/agreement articles should not exceed three pages, and clinical practice articles should not exceed three pages including text, figures, images and references.

k. The section for the "Letters to the Editor" should be formatted shortly and concisely, without any summary, and should be restricted in the number of references since it is mainly written to provide support or criticism over previously published articles.

l. Abbreviations should be written in the accepted international format and under parenthesis on the first mention and this abbreviation should be used throughout the text.

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Step-6: This is the step where the abstract is entered. Abstract should not exceed 200 words for case reports and reviews, and 250 words for research articles. Abstracts for research articles should include the following sections: Introduction, Material and Methods, Results and Conclusion.

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- Keywords (English)
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CONTENTS

EDITORIAL

Dear Colleagues,

We would like to start with our sincere wishes of happy spring time to you all. We also would like to congratulate the April 23th, the National Sovereignty and Children's Day, and upcoming May 1st the Labour and Solidarity Day. As you may know, The Turkish Thoracic Journal has been indexed by Emerging Sources Citation Index (ESCI) of Thomson Reuters, since January 2016, and we will start using Thomson Reuter's ScholarOne for online manuscript submission and peer review process very soon.

In this issue , there are five interesting original research papers on subjects such as "Neutrophil/Lymphocyte Ratio in COPD", "Tobacco Use in Dentistry Students", "Chronic Thromboembolic Pulmonary Hypertension", "HRCT and Pulmonary Tuberculosis", and "Respiratory Disability". We believe you will find the review on "History of Lung Transplantation", which is one of the first articles on the history of lung transplantation in Turkey, useful. We also hope that you will enjoy reading four very interesting case reports in this issue.

We look forward to meeting you with our next issue in July 2016.

With best wishes,

Editors
Hasan Bayram
Öner Dikensoy

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ORIGINAL INVESTIGATION

The Importance of Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is a common lung disease characterized by airflow limitation and systemic inflammation. Recently, neutrophil-to-lymphocyte ratio (NLR) has gathered increasing interest in the detection of inflammation in inflammatory diseases. This study aimed to investigate the role of NLR in COPD for identifying the detection of inflammation and recognition of acute exacerbation.

MATERIAL AND METHODS: The laboratory results of 103 COPD patients were included into the study, of which 47 patients were in acute exacerbation and 56 patients were at stable period, and there were 40 gender and age-matched healthy controls. Complete blood count (CBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were evaluated. NLR was calculated from CBC.

RESULTS: NLR values of patients with COPD (both acutely exacerbated and stable) were found significantly higher than those of the controls ($p< 0.001$, $p< 0.05$; respectively). In all patients with COPD, NLR values positively correlated with serum CRP ($r= 0.641$, $p< 0.001$) and ESR ($r= 0.276$, $p= 0.005$) levels and negatively correlated with forced vital capacity ($r= -0.20$, $p= 0.043$) and forced expiratory volume in the 1st second ($r= -0.288$, $p= 0.003$). For an NLR *cutoff* of 3.34, sensitivity for detecting exacerbation of COPD was 78.7% and specificity was 73.2% (AUC 0.863, $p< 0.001$).

CONCLUSION: Our results suggest that NLR may be considered as a reliable and simple indicator in the determination of increased inflammation in patients with COPD. Furthermore, NLR could be useful for the early detection of possible acute exacerbations in patients with COPD.

KEYWORDS: Chronic obstructive pulmonary disease, neutrophil-to-lymphocyte ratio, inflammation.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable common disease characterized by progressive and permanent airflow limitation associated with increased chronic inflammatory response of the lungs and airways against harmful gases and particles [1]. Especially cigarette smoke and inhalation of toxic gases cause chronic inflammation in the airways and pulmonary parenchyma in patients with COPD [2]. Exacerbation in COPD is frequently caused by respiratory tract infections, and the number of acute phase proteins and inflammatory cells in circulation during exacerbation increases [3-5]. However, it is known that there is an increase in some inflammatory markers and a low-grade systemic inflammation in some patients with COPD at the stable state [6]. It has been established in previous studies that various inflammatory markers like C-reactive protein (CRP), fibrinogen and leucocyte count increase in stable patients of COPD and that this increase is associated with the negative results of the disease [7-10]. Moreover, it has been described that elevated CRP levels can be used in the diagnosis of acute exacerbation and to approximate the prognosis of the disease [11,12].

Leucocyte count and its subtypes are well-known markers of inflammation [11,13]. Since the physiological response of the leucocytes in circulation against stress precipitates an increase in netrophile count and decrease in the lymphocyte count, the ratio of these two sub-groups to one another is employed in the intensive care practice[14]. In various recent studies, neutrophile-to-lymphocyte ratio (NLR) has been evaluated for its probable role in the inflammation periods of chronic diseases [15-17]. It has been seen that NLR is a sign of poor prognosis in patients who have undergone cardiovascular involvement and an independent determinant of mortality in patients with acute coronary syndrome [18,19]. In addition, increased NLR in patients with COPD has been identified a marker that could be used to determine inflammation, detect acute exacerbation in early stages, and it has also been confirmed that it could be an independent marker for all-cause mortality [20-22].

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The aim of this study was to evaluate the role of NLR in the identification of chronic inflammation and diagnosis of acute exacerbation in COPD and compare it with other traditional markers.

MATERIAL AND METHODS

Study Population

One hundred and eighty-two consecutive patients, who applied to the thoracic diseases polyclinic of our hospital with the diagnosis of COPD between June 1st, 2015 and September 1st, 2015, were enrolled to this retrospective study. Patients with COPD were determined using the data of our hospital's digital archive system. COPD diagnosis was confirmed by the results of the pulmonary function test (PFT). Thirty-one patients with a chronic respiratory disease apart from COPD, a pulmonary-extrapulmonary malignancy or a systemic disease that could affect leucocyte values, 26 patients whose leucocyte count was > 12 x 10^3/μL or < 4 x 10^3/μL, and 22 patients with insufficient PFT values were excluded from the study. As a result, a total of one hundred and three patients were included into the study, and the patients were analysed in two groups of "acute exacerbation" and "stable" as regards their clinical picture. Patients who had not had any significant changes in their symptoms in the last 3 months and the ones who did not need additional inhaler treatment dosages or any other additional treatments were defined as "stable COPD" [23]. Patients who had deterioration in the symptoms of the respiratory tract that caused change in medical treatment beyond normal daily variations were classified as "acute exacerbation"[1]. The duration of the disease, history of smoking, clinical data, hemogram, erythrocyte sedimentation rate (ESR), CRP and PFT results were recorded from the digital archive system of the hospital.

The control group included 40 healthy cases that were in the same age group as the patients with COPD and that applied to the thoracic diseases polyclinic for routine check and tests.

The present study was carried out in accordance with the Helsinki Declaration, and consent was received from the local ethics committee of our university.

Pulmonary Function Tests

Pulmonary function parameters (forced vital capacity [FVC] and forced expiratory volume in the first second [FEV_1]) were measured using standard spirometry device (Ultima CPX 790705-205; Medgraphics Corporation, St. Paul, MN, USA). FEV_1/FVC ratio was calculated. The obtained results were expressed as the percentage of absolute and expected values. Spirometric values were evaluated as regards the standards specified by the European Respiratory Society [24].

Determination of Neutrophil-to-Lymphocyte Ratio

All blood samples were put in tubes with potassium EDTA for blood count. Hemoglobin, hematocrit, thrombocyte, and white blood cell and type (neutrophile, lymphocyte, eosinophile and monocyte) were identified with automatic blood count device (Siemens Advia 2120, Diagnostic Solutions, Milan, Italy) by electrical impedance method. NLR was obtained by dividing the neutrophile count in the hemogram blood to the lymphocyte count.

Statistical Analysis

IBM SPSS Statistics 21 (Statistical Product and Service Solutions 21.0 version, authorization code: d91314f638c364094170; Armonk, NY, USA) Package was used for the statistical analysis in this study. The results were given as mean ± standard deviation. p value < 0.05 was considered statistically significant. Student's t-test was used for the comparison of two independent groups. OneWay Anova test was used for the comparison of multiple groups. Tukey test was used to test the significance of any observed difference. Chi-square (X^2) test was carried out to compare gender distribution between the groups. Pearson correlation test was used to evaluate parametric values. ROC curve was drawn to show the specifity and sensitivity of NLR.

RESULTS

A total of 103 patients with COPD, of whom 47 (45.6%) were in the exacerbation state and 56 (54.4%) were at the stable period, and 40 healthy controls were evaluated in the study. No statistically significant difference was found among the three groups in terms of age and gender. Neutrophile, lymphocyte and NLR levels were detected statistically significantly high in both COPD groups when compared to the control group. Moreover, NLR was detected statistically significantly high in the COPD exacerbation group when compared to the stable patients with COPD. While no difference was determined between both COPD groups in terms of ESR, CRP levels were found to be statistically higher in the exacerbation group. When only COPD groups were included into the analysis, the duration of the disease was found statistically significantly high in the exacerbation group, and FVC and FEV_1 levels were found low. Clinical and laboratory data of the three groups and the duration of the disease, smoking state, and PFT data of the patients are given in Table 1.

When all patients with COPD included into the study were incorporated into the correlation analysis, it was observed that there was a good degree of positive correlation between NLR and CRP levels and a poor degree of positive correlation between ESR levels (r= 0.641, p< 0.001; r= 0.276, p= 0.005 respectively) (Figure 1). Furthermore, it was detected that there was a poor degree of negative correlation between NLR and FVC levels and a poor-medium degree of negative correlation between FEV_1 levels (r= -0.20, p= 0.043; r= -0.288, p= 0.003, respectively) (Figure 2).

When NLR was evaluated with ROC analysis to estimate exacerbation in patients with COPD, the area under the ROC curve was detected as 0.863 (95% Cl 0.796-0.931; p< 0.001). In addition, the sensitivity and specifity of NLR were found as 78.7% and 73.2%, respectively when the optimal cut-off value was specified as 3.34 in terms of estimating exacerbation (Figure 3).

Table 1. Clinical and laboratory findings of the study groups and the results of the pulmonary function test

	COPD (Exacerbation) (n= 47)	COPD (Stable) (n= 56)	Control (n= 40)
Age (years)	67.8 ± 10.1	65.6 ± 8.7	63.6 ± 8.7
Gender (male, n (%))	38 (80.9)	44 (78.6)	30 (75)
Cigarette (pack-year)	42.76 ± 21.78	40.35 ± 19.79	-
Duration of the disease (year)	8.65 ± 2.82 [a]	6.21 ± 2.73	-
Laboratory findings			
Leucocyte (10^3/μL)	8.96 ± 2.03 *,[b]	7.83 ± 1.67	7.05 ± 1.43
Neutrophil (10^3/μL)	6.66 ± 1.93 *,[a]	4.77 ± 1.24***	3.88 ± 0.82
Lymphocyte (10^3/μL)	1.34 ± 0.53 *,[a]	2.01 ± 0.75****	2.38 ± 0.58
NLR	5.78 ± 3.14 *,[a]	2.67 ± 1.13****	1.68 ± 0.41
Hemoglobin (g/dL)	14.65 ± 2.13	14.58 ± 1.78	14.2 ± 1.86
Platelet (10^3/μL)	264.9 ± 103.7	248.6 ± 82.1	253.2 ± 69.6
ESR (mm/saat)	27.10 ± 21.41*	20.05 ± 15.41**	7.97 ± 5.80
CRP (mg/L)	48.18 ± 45.14*,[a]	19.41 ± 28.42****	3.84 ± 1.18
Pulmonary Function Tests			
FVC, %	46.95 ± 12.50 [b]	56.96 ± 16.25	-
FEV_1, %	34.55 ± 11.08 [b]	43.05 ± 15.05	-
FEV_1/FVC	55.31 ± 10.49	56.42 ± 10.77	-

NLR: Neutrophil-to-lymphocyte ratio; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; FVC: Forced vitalcapacity; FEV_1: Forced expiration 1st second volume. The results were given as mean ± standard deviation.
* p< 0.001, ** p< 0.005, *** p< 0.01, **** p< 0.05; when compared to the controls[a]
p< 0.001,[b] p< 0.005; when compared to the patients with stable COPD.

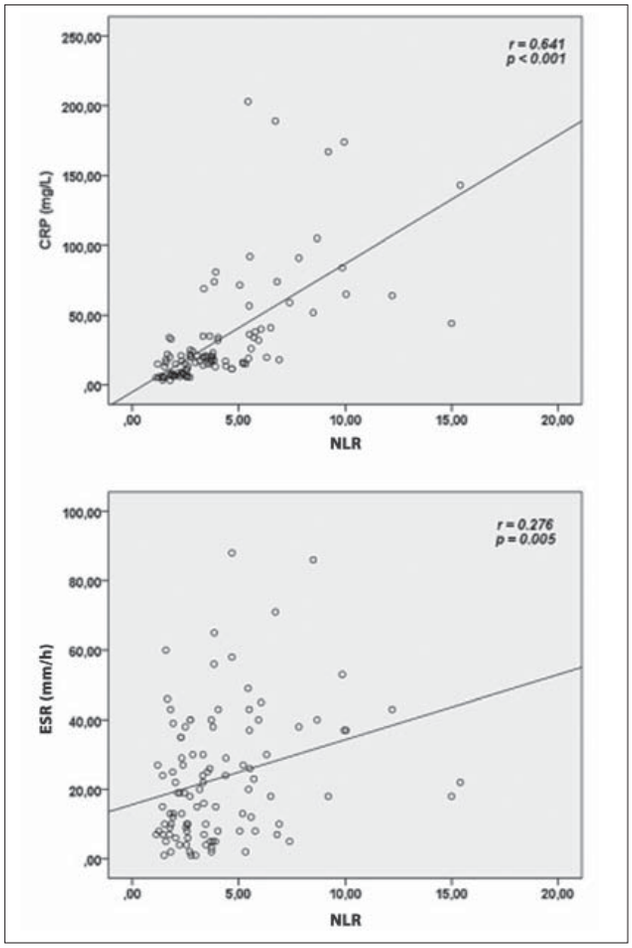

Figure 1. Correlations between neutrophile-to-lymphocyte ratio (NLR) and serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

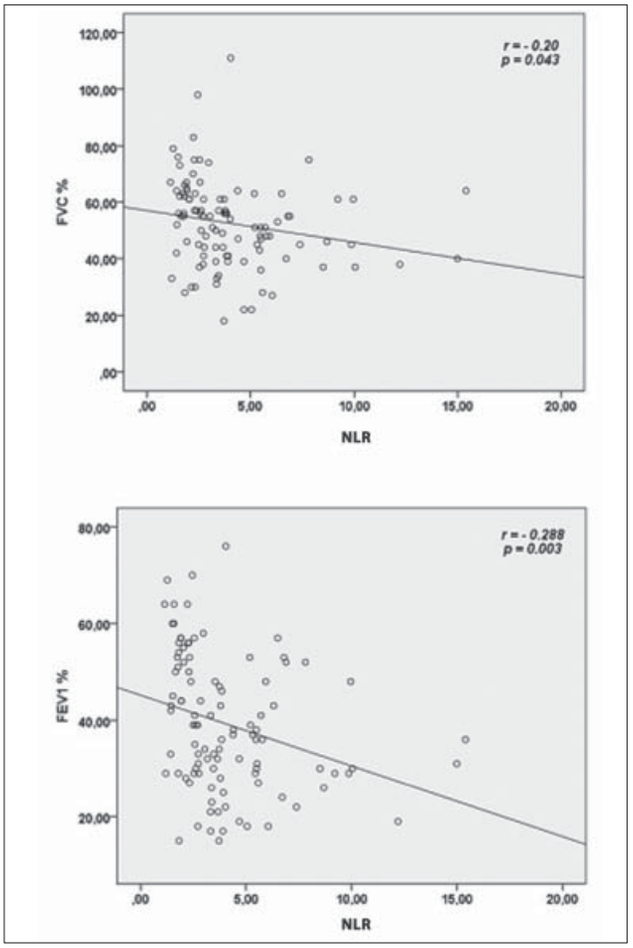

Figure 2. Correlations between neutrophile-to-lymphocyte ratio (NLR) and forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1).

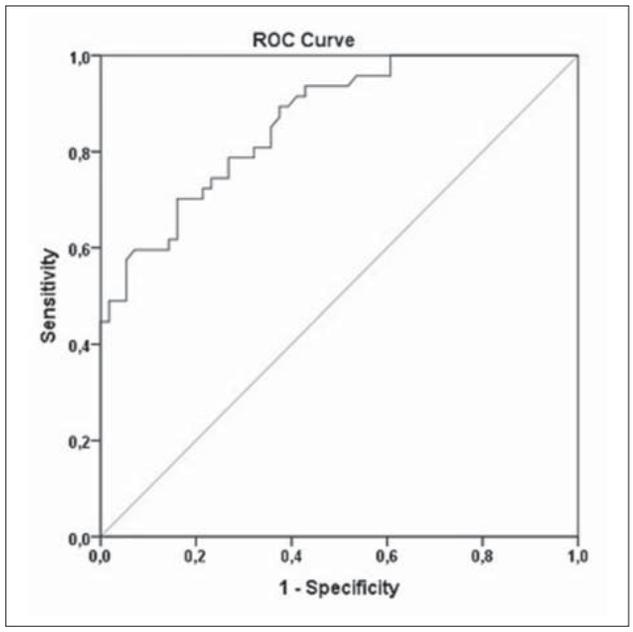

Figure 3. ROC curve indication of the ability of neutrophil-to-lymphocyte ratio in estimating exacerbations in patients with COPD.

DISCUSSION

It was detected in this retrospective study that NLR levels were higher in acute exacerbation or stable patients with COPD when compared with the healthy controls. Additionally, it was seen that there was a positive correlation between NLR levels and CRP and ESR levels, and that NLR had a significant specificity and sensitivity in terms of estimating exacerbation.

A set of markers that could be measured in the blood and that could show the presence/severity of an infection and inflammation has been already identified. These can be used as early and sensitive indicators in determining the infective picture. Parameters, such as serum CRP level, ESR value, leucocyte count, and neutrophile dominance in the leucocyte formula are quite frequently used parameters while following infection in clinical practice [25]. Pathological processes are not specifically localised to the lungs. COPD is a chronic inflammatory disease with high commorbidity and systemic involvement associated with conditions like metabolic syndrome, osteoporosis, diabetes, and cardiovascular diseases [26]. Levels of various inflammation markers like CRP, fibrinogen and leucocyte count have been detected to rise in COPD patients in the exacerbation period [3-5]. Additionally, it is known that acute phase proteins and other inflammatory cytokines increase even in stable patients with COPD and that there is a low-grade chronic inflammation [27]. This chronic inflammatory period seen in patients with COPD has an important role in the pathogenesis of the disease [6]. Furthermore, it has been established that these elevated inflammation markers are associated with the poor prognosis of the disease and with the increase in the commorbidity ratios [7-10]. The best known among these markers is CRP. Elevated systemic CRP levels have been found associated with the increase in disease severity, deterioration in health condition, hospitalization, and mortality rates in COPD [8,28,29]. In our study, CRP and ESR levels were found higher in both COPD groups when compared with the controls. Moreover, CRP levels were detected higher in patients of COPD at the exacerbation state when compared to the stable ones. It is known that the most frequent cause of exacerbation in patients with COPD is infections. In patients at exacerbation state, CRP values may have been notably elevated depending on infections. However, elevated CRP levels even in stable COPD patients suggest systemic inflammation in these patients.

The presence of chronic inflammation in central and peripheral airways along with an increase in various inflammatory cell types and proinflammatory mediators is a fundamental characteristic of COPD. Inflammation causes damage to the lung parenchyma and contribute to the evidencing of airway limitation. It is known that neutrophils, macrophages and CD8 T-lymphocytes are important inflammatory cells in COPD [30]. It is thought that neutrophils play a role as responsible key cells of lung damage in emphysema [31]. Neutrophil count in circulation rises in systemic inflammation. Elevated neutrophil count is associated with the progression of COPD [32]. Recently, NLR has caught the interest of many researchers as an inflammatory marker. NLR has been shown in various studies to be a prognostic marker in several inflammatory diseases, such as cardiovascular diseases, kidney disease and familial Mediterranean fever [15-19]. As regards our research, there are 4 studies in the literature which investigate the importance of NLR in patients with COPD. Günay et al. [20] have retrospectively analyzed 178 stable patients with COPD, 91 patients with COPD in the acute exacerbation period and 50 control cases. NLR value has been found notably higher in both COPD groups in their study when compared to the controls. Moreover, NLR has been detected statistically significantly higher in patients with COPD in the exacerbation period when compared to the stable ones. In addition, it has been observed in their study that there is a positive correlation between NLR and CRP levels. In a prospective study where 386 mild and severe COPD patients have been followed-up for 10 years, NLR has been detected as an independent marker for elevated all-cause mortality [22]. It has been expressed in a retrospective study where 140 stable patients with COPD and 50 controls have been included that NLR could be a simple, effective and practical indicator in the early detection of metabolic syndrome [33]. In another study where 100 patients with COPD first in the acute exacerbation period and then at the stable period and 50 controls were evaluated retrospectively, NLR has been shown to be a marker that could be used to detect elevated inflammation like CRP, leucocyte count and ESR [21]. It was detected similarly in our study that NLR levels were higher in patients with COPD at the exacerbation and table period when compared to the controls. When all patients with COPD were taken into consideration, a positive correlation was observed between NLR, ESR and CRP. Moreover, it was determined that NLR had high specifity and sensitivity in estimating acute exacerbation. Our results suggest that NLR could be used as an inflammatory biomarker in showing acute exacerbation and chronic inflammation.

It has been previously reported that the decrease in pulmonary functions is associated with the increase in the inflammatory markers [34]. However, the relation of NLR with pulmonary functions has not been sufficiently examined in the literature. Yasar et al. [33] have detected a negative correlation between NLR and FEV_1 levels but a positive correlation between between dyspnea score. In our study, a negative correlation was detected between NLR level and both FVC and FEV_1 levels. This results makes us think that the more severe the COPD is, the more severe the inflammation is and that NLR could be a practical marker to estimate inflammation severity.

Limitations to the Study

This is not a prospective study. It is a retrospective study that made use of the digital archive system of our hospital. Therefore, data like COPD evaluation test, mMRC dyspnea scale and previous exacerbation history could not be reached, and thus the patients could not be classified into recent COPD classification. In addition, as the echocardiography and arterial blood gas results of the patients were insufficient, these data were not analyzed in our study. Similarly, patients who lacked the data fundamental for the study were also excluded from the study. Furthermore, in terms of estimating exacerbation in patients with COPD, it would be more correct to evaluate NLR levels both at the stable and the exacerbation period in the same patient group to detect the significance of NLR since NLR levels could be varying like other inflammation markers while specifying cut-off values.

CONCLUSION

Overall, NLR levels in our study were detected higher in stable patients with COPD and in patients at the exacerbation period when compared to the controls, and they correlated with traditional inflammation indicators. NLR could be a useful and practical inflammation marker to estimate acute exacerbation in patients with COPD and to detect potential inflammation at the stable period.

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ORIGINAL INVESTIGATION

The Prevelance of Tobacco Use and the Factors Influencing in Students Studying at Two Dentistry Faculties in Turkey

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Abstract

OBJECTIVES: The objective of this study was to determine the pattern and effects of tobacco and tobacco products use among students of dentistry.

MATERIAL AND METHODS: A cross sectional study was performed in the Dentistry Faculty of Ege and Dicle Universities between April and May 2013. All freshmen and senior year students receiving education in both universities were included into the study (n= 321). A questionnaire consisting of 26 questions was used to determine the smoking habits of the students and the influencing factors regarding this habit. Students replied the questions under supervision.

RESULTS: A survey was conducted among 298 students out of 321 who were attending both universities. 46.6% of the participants were female and 53.4% were male. Smoking prevelance of the students was 29.9%. It was 19.9% in freshmen students and 45.8% in senior students. According to the first class of students in the fifth grade students in the prevalence of smoking in was found to be highly statistically significant ($p< 0.001$). Among other tobacco products the following was identified as mostly used: waterpipe, also known as narghile (27.4%), cigarwraps (9.7%), cigar (9.4%) and smoking pipe (2.0%). While 22.5% of the students stated that they started smoking after the age of 15, 36.0% started between the ages of 15 and 18 and 41.5% after the age of 19. The rate of smoking in the house was significantly higher ($p< 0.001$) among smokers than non-smokers. While 78.7% of the students stated that they would like to quit, 64.3% tried once or more to quit.

CONCLUSION: Smoking habit was found to be higher among medical students than the social average. Smoking is more frequent in higher classes. From early years onwards, students of dentistry should be intensively educated regarding the harmful effects of tobacco on health, and efforts should be made to prevent and control of tobacco epidemic.

KEYWORDS: Dentistry, student, tobacco, cigar

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INTRODUCTION

Tobacco use is a major public health problem in the world, and especially in developing countries [1-3]. It is estimated that there are 1.3 billion smokers worldwide, and if no intervention is carried out, this number will reach 1.7 billion in 2025 [4]. Tobacco and tobacco products rank first among the causes of preventable death. Standard cigarettes are the most commonly consumed tobacco type. 5.4 million people die of the use of these products every year, and it is expected that this number will rise to 8 million in 2030 [5]. Physicians, dentists and other health professionals socially play an increasing and vital role in diminishing the risk of tobacco-related health issues [6].

It has been reported in the studies conducted overseas that the prevelance of tobacco use among the health personnel is lower than that of the general population in the same age group [7-9]. However, it is seen Turkey that the prevelance of tobacco use is high in general and that health professionals have a similar rate of tobacco use with that of the general population [10]. It has been detected in various studies that health professionals usually start smoking in their years as students [8,9,11,12].

It is seen that physicians, dentists and nurses who are expected to contribute to the control of tobacco and tobacco products have a high prevelance of tobacco use and that this prevelance is not different from that of the general population[4,5,10]. It was reported that the prevelance of smoking among physicians was lower in countries that were successfull in reducing the habit of tabacco consumption [13,14].

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While Smith et al. have stated in a study they carried out among students of dentistry in 19 countries that the rate of tobacco use is under 10% in modern countries, such as Canada (3%), the United States of America (4%), Brazil (6%), and England, the same rate is under 20% in countries like India (10%) and Australia (13%) [15]. The same researcher has indicated that nearly half of the students of dentistry in countries like France (33%), Bulgaria (34%), Serbia (43%), and Greece (47%) use tobacco products.

The curriculum of many dentistry faculties in Europe include the telling of the harmful effects of tobacco products to students, and students are asked to take active part in the control of tobacco [16].

This study was conducted in two different dentistry faculties (Dicle and Ege Universities) of Turkey with the purpose of determining tobacco use among freshmen and senior year students of dentistry, who will have a vital part in the control of tobacco in the future and identifying the factors affecting its use.

MATERIAL AND METHODS

This cross-sectional study was carried out in the Faculties of Dentistry of Ege and Dicle Universities between April and May, 2013. All freshmen and senior year students of both faculties were included into the study (n= 321). The reason for choosing these two faculties was due to the fact that the researchers worked in these faculties, and thus, necessary permissions were easier to receive.

The Variables of the Research

Dependent variable: The state of using tobacco products. It was grouped as defined below.

Users of tobacco products: The students who stated that they smoked 5-10 cigarettes and/or cigarwraps a week, the ones that smoke waterpipe, pipe and cigar once or twice a week, and the ones that regularly smoked.

The ones that quit smoking: The students who had not smoked in six months.

The ones who tried smoking: The students who tried smoking but are not currently smoking.

Non-smokers: The students who had never smoked.

Independent variables: Age, gender, the age to start using tobacco products, the duration of use, the cessation of use, the state of tobacco use in the house, the presence of school policies regarding tobacco products.

The data were collected through a questionnaire consisting 26 questions, to which the students replied under supervision.

Statistical analysis: SPSS for Windows 15.00; SPSS Inc,. Chicago, IL, USA package program was used to analyze the data. Continuous variables and rates were analyzed with t-test and chi-square test, respectively.

Written permission was obtained from the authorized committees of the faculties where the study was carried out. Informed consent was taken from the students who wished to participate in the study, and the questionnaire was filled out by the students themselves.

RESULTS

Out of the 321 freshmen and senior year students between the ages of 17 and 28, who receive education in the dentistry faculties of Ege and Dicle Universities, 298 (92.8%) participated in the study. Mean age of the students was 20.93 ± 2.35, and 184 (61.7%) of them were from the dentistry faculty of Ege University and 114 (38.3%) from Dicle University. The freshmen and senior year students of both faculties included 180 (60.4%) and 118 (39.6%) students, respectively, and 139 (46.6%) of these students were females and 159 (53.4%) were males.

Eighty-nine (29.9%) of the students included into the study were using tobacco products. 19.4% of these students were females and 39.0% were males, and a statistically significant difference was detected between gender and tobacco product use, which was higher in males ($p< 0.001$). 32.6% and 25.4% of the students using tobacco products were from Ege and Dicle Universities respectively, and a significant difference was not detected as regards the state of tobacco product use between the two universities ($p< 0.189$). 19.4% and 45.8% of the students of both faculties using tobacco products were freshmen and senior year students respectively, and it was determined that senior year students use more tobacco products significantly ($p< 0.001$). When the smoking state of the freshmen and senior year students of both universities were considered, the freshmen and senior year rates were found respectively as 21.6% and 49.3% ($p< 0.001$) for the Dentistry Faculty of Ege University, whereas the same rates were found respectively as 15.6% and 40.0% for the Dentistry Faculty of Dicle University. The difference was found statistically significant among the freshmen and senior year students of both faculties ($p< 0.001$, $p= 0.004$ respectively).

Presence of someone using tobacco and tobacco products in the houses or the places where students that use tobacco live was 48.3%, tobacco use of the guests with/without permission was 67.4% and tobacco use in every room of the house or in an exclusive place for tobacco consumption was 64.4%. The rate of tobacco use indoors in the school was detected as 12.1%. These rates were higher than the same circumstances of students who do not use tobacco, and a statistical difference was detected.

Seventy of the 89 students using tobacco (7.7%) stated that they were thinking of quitting. Forty-five of these 70 students (64.3%) had attempted to quit smoking once or more than once. Twenty-three of the students who attempted to quit smoking (51.4%) indicated that they had tried to quit smoking in the last one year. When factors affecting the decision of quitting smoking was considered, it was seen that 71.1% of the students attempted to quit smoking as a result of their own decisions, 17.9% as a result of the effect of family and friends, 4.4% as a result of medical issues, 2.2% as a result of indoor prohibition, and 4.4% as a result of

having been influenced by the public service advertisements shown on television. Twelve of the 70 students who were thinking of quitting smoking (17.1%) stated that they used a scientifically proven method (Table 1).

When students using tobacco products were assessed as regards the state of tobacco product use, the rate of the students who had never used tobacco products was 49.0%, the rate of regular users was 18.2%, the rate of occasional users (5-10 cigarettes a week) was 11.7%, the rate of the students who had tried tobacco was 18.5%, and the rate of quitters was 2.7%. The prevelance of use of other tobacco products besides cigarettes was as follows: waterpipe (27.4%), cigarwraps (9.7%), cigar (9.4%), and pipe (2.0%) (Table 2).

When the age to start using tobacco was considered, it was determined that 22.5% of the students started using tobacco before the age of 15, 36.0% between the ages of 15 and 18, and 41.5% after the age of 19. It was seen that the prevelance of tobacco use also increased with increasing age, which was statistically significant ($p< 0.001$). 25.8%, 66.3% and 7.9% of these students stated that they had been using tobacco for a year, 2-5 years, and for 6 years and more, respectively. 28.1%, 34.8% and 37.1% of the students stated that they preferred local, foreign and both brands, respectively (Table 3).

DISCUSSION

The rate of tobacco use among the students included into the study (29.9%) was higher than the rate of tobacco use in Turkey (27.1%)[17].

Keskinler et al. found in a study they conducted in 9 faculties of Atatürk University in 1999 that the rate of smoking of dentistry students was 43.9%, which was the highest rate among the students of other faculties [18]. Since our study found the rates of tobacco use lower than the study of Keskinler et al. which was conducted 14 years prior to ours, it was interpreted that there was a decrease in tobacco use among dentistry students parallel to the decrease in tobacco use in the society with the help of the tobacco control studies carried out until today. However, Kaptanoglu et al. detected in their study investigating the state of smoking of students of Marmara University in 2012 that the rate of dentistry students smoking regularly every day was 18.9% (19). The rate of dentistry students smoking regularly every day was found as 18.2% in our study, which is similar to that of Kaptanoglu et al.'s. It is seen that there has been no change in the rate of tobacco use among dentistry students in the last two years. According to Turkey 2012 Global Adult Tobacco Research report, regular tobacco use every day was 23.8%, which was a higher rate than that of the dentistry students determined in the study [17].

Table 1. The factors affecting the state of smoking of the students studying in both dentistry faculties

	State of smoking						p
	Smokers* (n= 89)		Non-smokers (n= 209)		Total (n= 298)		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%[b]**	
University							
Ege	60	32.6	124	67.4	184	61.8	0.189
Dicle	29	25.4	85	74.6	114	38.2	
Gender							
Female	27	19.4	112	80.6	139	46.6	0.001[a]
Male	62	39.0	97	61.0	159	53.4	
School year							
Freshmen	35	19.4	145	80.6	180	60.4	0.001[a]
Senior	54	45.8	64	54.2	118	39.6	
Use of tobacco products in the house							
None	36	23.4	118	76.6	154	51.7	0.007
Existent	53	36.8	91	63.2	144	48.3	
The state of tobacco use of the guests in the house							
Not allowed	17	17.5	80	82.5	97	32.6	0.001
Smokes by receiving permission	37	28.0	95	72.0	132	44.3	
Smokes by not receiving permission	35	50.3	34	49.3	69	23.1	
Where it is smoked in the house							
Not smoked in the house	15	14.2	91	85.8	106	35.6	0.001
Private place in the house	38	28.8	94	71.2	132	44.3	
Everywhere	36	60.0	24	40.0	60	20.1	
Use of tobacco products in the school							
Not allowed indoors	72	27.5	190	72.5	262	87.9	0.004
Allowed in private places	17	47.2	19	52.8	36	12.1	

* The students stating that they smoke everyday and on occasion were accepted as smokers.
[a] Chi-square test.
[b] Column percentage.

Table 2. The range of students using tobacco and tobacco products as regards the type of tobacco and its prevelance of use

	The use of tobacco product				
Tobacco product	**Never smoked n (%)**	**Constantly smoke n (%)**	**Smoke on occasion* n (%)**	**Tried n (%)**	**Quit n (%)**
Cigarette	146 (49.0)	54 (18.2)	35 (11.7)	55 (18.5)	8 (2.7)
Waterpipe	165 (55.4)	1 (0.3)	81 (27.1)	51 (17.1)	-
Pipe	288 (96.6)	1 (0.3)	5 (1.7)	4 (1.3)	-
Cigar	260 (87.2)	-	28 (9.4)	10 (3.4)	-
Cigarwraps	261 (87.6)	3 (1.0)	26 (8.7)	8 (2.7)	-

* Cigarette-cigarwraps (5-10 times a week), waterpipe-pipe-cigar (1-2 times a week).

Table 3. The characteristics of cigarette use of students who use tobacco products

Characteristics (n= 89)		**n**	**%**
The age to start smoking	< 15	20	22.5
	15-18	32	36.0
	≥ 19	37	41.5
The duration of smoking (year)	< 1	23	25.8
	2-5	59	66.3
	> 5	7	7.9
Daily cigarettes	1-5	10	11.2
	6-10	31	34.8
	11-15	22	24.8
	16-20	15	16.8
	> 20	11	12.4
The type of cigarettes	Local	25	28.1
	Foreign	31	34.8
	Both	33	37.1

It was detected in the present study that one in every five freshmen year students (19.4%) and one in every two senior year students used tobacco products. It was seen in the dentistry students of these two faculties that tobacco use had risen over the years. This situation makes us think that they do not receive adequate education regarding the control of tobacco during their years in the faculty. In a review study of Tezcan et al. where they have investigated the state of smoking among physicians, nurses and medical school students in 22 health institutions in Turkey, they have specified that the smoking prevelance of medical school students in their first year is 10.4%, 27.9% in their fourth year and 29.1% in their last year. It is seen that just as in dentistry students, the rate of smoking has risen over the years in medical school students [10].

Another interesting finding in the literature is that the rate of smoking of dentistry students of Mediterranean countries like Italy (33%), France (33%) and Greece (47%) is higher than that of the dentistry students in other European countries (England (7%), the Netherlands (24%), Ireland (20%)) [4,1,15,20]. In a review study by Smith et al. where they have investigated the rates of smoking in students of the dentistry faculty in 19 countries, they have indicated that male students smoke more than female students in all countries [15]. When studies conducted on medical school students in various universities in our country are evaluated, it has been shown that the rate of smoking in male students ranges between 18-48% and between 5-29% in female students [4,5,10,21]. In our study, the rate of smoking in female students was found as 19.4% and as 39.0% in male students. Male students smoked more than female students, and these findings were found similar to the data of the study. Moreover, according to the 2012 report of global adult tobacco research, the rate of smoking among the female gender was found as 13.1%. The rate of tobacco use in the female students in our study (19.4%) is higher than this rate [17].

Although cigarette is the most frequently consumed tobacco product, studies have shown that waterpipe use has increased in recent years [22-24]. The second most used tobacco product among the students in our study was also waterpipe. In a study by Ozcebe et al. including 5221 students from various universities, the use of waterpipe has been found as 20.8% [22]. Korkmaz et al. have determined that the use of waterpipe among the students of Suleyman Demirel University is 26.9% [25]. The prevelance of waterpipe use among the students of our study was found as 28.1%. These rates are almost similar to those of smoking. Such a high rate of waterpipe use among university students is remarkable.

13.4% of the students participating in our study stated that they had smoked cigarwraps or tried at least once. It was seen that cigarwraps ranked third among the most used tobacco products. Hassoy et al. confirmed in a 2011 study conducted on students of vocational school of health that 17.5% of the participants to the study had tried cigarwraps at least once [26]. Similarly, although the students within the scope of the research stated that they did not smoke cigars constantly, it was detected that the rate of smoking cigars once or twice a week was 9.4%. One student said that he/she smoked pipe regularly and five students (1.7%) said that they smoked pipes on occasion. In the common question about smoking pipe-cigar, Korkmaz et al. have found the smoking rate as 7.5% and detected that this rate was lower when compared to the consumption of other tobacco products [25]. Similarly in our study, smoking pipe and cigar is lower among dentistry students when compared to other tobacco products.

It has been shown in various studies that the age to start smoking in our country ranges between 13-17 [2-5]. When the age to start smoking was evaluated in our study, it was detected that 22.5% of the students started using tobacco products when they were under the age of 15 and 36.1% of the students started using tobacco products between the ages of 15 and 18, which shows that one-third of the students started using tobacco products before they enrolled in the dentistry faculty and that two-third of the students started using tobacco products after they enrolled in the dentistry faculty. This situation is consistent with the study by Demirel et al., which shows that 41.3% of the female students, 16.9% of the male students and 24.3% of all students have started smoking in the freshmen and sophomore years in Erciyes University [27]. The impact of starting university on the use of tobacco products must be questioned and necessary measures must be taken in this regard.

Presence of another individual using tobacco products and the prevelance of another individual using tobacco products indoors in the settings where students using tobacco products lived were found statistically significantly higher when compared to the students not using any tobacco products. There are studies demonstrating that the presence of a tobacco product user in the house encourages the other members of the household to start using these products [28-30]. In this context, the data of the study support that the students using tobacco products live in settings where there are persons with similar habits.

Four (78.7%) of every five students using tobacco products in the study wanted to quit using tobacco. It was seen that 71.1% of the students attempted to quit smoking as a result of their own decisions, 64.3% of the students had attempted to quit smoking once or more, 51.4% had attempted to quit smoking in the last one year, and 17.1% had attempted to quit smoking with a scientifically proven method. The multitude of the dentistry students who wish to quit using tobacco products is remarkable. When the year the study was conducted is taken into consideration, it can be thought that tobacco control studies like smoke-free zone which has begun a while before this date have increased awareness. However, since only 17.1% of the students attempted to quit smoking with a scientifically proven method, it is our opinion that the familiarity of these methods among students is very low. Similarly, the study by Demirel where only 16 (4.5%) of the students who have wanted to quit smoking have considered receiving help from a professional institution supports our aforementioned opinion [27].

There are many studies within the scope of law no. 4207 regarding tobacco control in our country. According to this code, it is forbidden to use tobacco and tobacco products in schools, hospitals, public transportation vehicles, and indoors. The finding of our study suggesting that there is a 12.1% rate of tobacco product use indoors despite being forbidden shows that even indoor prohibition is violated.

CONCLUSION

The prevelance of tobacco use in students receiving education in the field of health is higher than that of the general public. The prevelance of tobacco use increases with each school year. The students need to be thoroughly educated on the negative effects of tobacco use on health and control of tobacco use as of the first semester.

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ORIGINAL INVESTIGATION

The Incidence and Related Risk Factors of Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism

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Abstract

OBJECTIVES: More than half of (> 50%) the patients with choronic thromboembolic pulmonary hypertension (CTEPH) have no acute pulmonary embolism history with clinical signs, so determining the actual incidence and prevalence of CTEPH is difficult. This study aimed to investigate the incidence of CTEPH and the risk factors that may be associated with CTEPH in patients with acute pulmonary thromboembolism (PTE).

MATERIAL AND METHODS: Three hundred and eighteen patients with acute pulmonary embolism diagnosed by thorax CT or ventilation/perfussion scintigraphy in our clinic were included into this study. Patients with risk factors for pulmonary hypertension other than thromboembolic disease were excluded from the study. Patients with pulmonary hypertension (PHT) (systolic PAB > 35 mmHg) determined by echocardiography performed in the 6th month were enrolled into the study.

RESULTS: Fifty-seven of the 112 patients were female, and the mean age was 57.09 ± 17.30 (16-86) years. Presence of PHT was determined in the 6th month in 45 of the 112 patients (8 of them were symptomatic) and CTEPH incidence (symptomatic + asymptomatic) was identified as 40.16%. Symptomatic CTEPH incidence was calculated as 7.14%. When we searched about the risk factors that may have a role in the development of CTEPH; we determined that CTEPH risk was increased 4.59 times by only being male (95% CI 1.071-19.683, p= 0.040), 218 times by previous history of DVT (95% CI 1.235-38543.073, p= 0.041), and 56.903 times by PaO_2 < 80 mmHg (95% CI 2.656-1219.228, p= 0.010).

CONCLUSION: CTEPH development after PTE is a situation that can occur in many patients. If probable risk factors are known, patients can be closely monitorized for CTEPH development.

KEYWORDS: Pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension, incidence, risk factors

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INTRODUCTION

Pulmonary thromboembolism (PTE), which is defined as the travel of clots from systemic deep veins to the pulmonary vascular bed, is a commonly encountered but difficult to diagnose disease with high mortality [1]. Substances, such as serotonin, which is released when PTE develops, arachidonic acid metabolites, peptidoleukotriene, platelet activating factor (PAF), and platelet-derived growth factor (PDGF) are vasoconstructive agents. These substances contribute to the increase in pulmonary vascular resistance (PVR) by creating stenosis in the pulmonary vascular bed and to the development of vasospasm through reflex by affecting the receptors in the vein wall [2]. Pulmonary artery pressure is elevated with the increase in PVR.

After an acute PTE attack, full resolution of the thrombus and restoration of the pulmonary vascular bed occur in 4 to 8 weeks [3]. However, full resolution has been reported only in 50-80% of the cases [4]. As a result of obliteration of the pulmonary vascular bed due to recurrent and organised PTE, chronic thromboembolic pulmonary hypertension (CTEPH) occurs. In order for a patient to receive CTEPH diagnosis, he/she should receive anticoagulant treatment for at least 3 months [5]. The incidence of CTEPH development after acute pulmonary embolism has been reported as 0.5-3.8% [6]. However, having no history of acute pulmonary embolism that gives clinical symptoms in more than 50% of the patients with CTEPH makes it difficult to specify the true incidence and prevelance of the disease. Diagnosis is usually made in the advanced stage since dyspnea, which is a primary symptom of the disease, is present in most patients. Diagnosis can be delayed if physical examination is normal in early stages. Patients can be asymptomatic even

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when serious pulmonary hypertension develops. Therefore, CTEPH should be considered in patients undergoing a PTE attack and whose symptoms do not decrease despite anticoagulant treatment, and diagnosis should be confirmed with techniques like echocardiography and CT. In CTEPH etiology, the presence of thrombophilic factors is an unequivocal opinion, lupus anticoagulant and anticardiolipin anticores are positive only in 10-24% of the cases, and while factor V Leiden mutation is encountered in a 4-6.5% rate, protein C, protein S and antithrombin deficinecies are seen in a rate less than 0.5% [7,8].

The objective of this study was to investigate the frequency of CTEPH in patients with PTE and determine the risk factors associated with the development of CTEPH. It is our belief that CTEPH that could develop after a PTE attack can be foreseen with the detection of risk factors.

MATERIAL AND METHODS

Patients admitted to the Pulmonology Clinic of Firat University with a diagnosis of PTE between December 2010 and June 2013 were included into this study. The study was approved by the ethics committee of our university. Written consents were received from all patients who participated in the study. The study was planned to be prospective. The patients were followed for 6 months.

Patient Selection

Acute PTE diagnosis was made either by seeing hypodense filling defects in the vein lumen on thoracic CT angiography or by reporting ventilation/perfusion scintigraphy as 'high probability' in patients with a high clinical probability. Apart from thromboembolic diseases, patients with COPD, diffuse interstitial lung disease, sleep breathing disorders, systemic diseases (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis), collagen tissue disease, congenital heart disease, left ventricle failure or valvular heart disease were excluded from the study.

Arterial blood gas (ABG), D-Dimer and troponin levels of the patients on admission were assessed, and lower extremity venous Doppler USG tests were carried out. Computed tomography pulmonary angiography (CTPA) and ECHO examinations were performed both upon admission and in the sixth month follow-up.

Computed tomography pulmonary angiography: CTPA was performed by using 64 multislace sacnner (Toshiba). 100 m Liopromid was used during filming.

Echocardiography: Echocardiography was carried out by sing 3.4 MHz transducer probe with two dimensional, classical and tissue Doppler. Patients, whose systolic pulmonary artery pressure was (sPAB) > 35 mmHg on the echocardiographic examination carried out in the sixth month, were considered as CTEPH [9,10]. Systolic pulmonary artery pressure was calculated by using Bernoulli equation and evaluating tricuspid regurgitation pressure gradient (TIPG = 4 x tricuspid regurgitation velocity 2) in addition to right atrial pressure.

Arterial blood gas: ABG samples taken from the radial artery in room temperature were studied by blood gas analysis device (Rapidlab 348. Biobak. Bayer Diagnostic, UK).

D-dimer and troponin levels: 5cc venous blood was taken for D-dimer and troponin levels and its quantitative analysis was studied in autoanalyzer (Immulite 2000) with "chemiluminescent enzyme immunometric" method on Siemens kit.

Statistical Analysis

SPSS 16.0 computer program was used for the analysis of data. The results were presented as mean ± standard deviation. $p< 0.05$ values were considered statistically significant. When comparing the data of the patients with CTEPH and without CTEPH, student's t-test was used for the ones showing normal distribution and Mann-Whitney tests was used for the ones not showing normal distibution. Chi-square test was used in the evaluation of non-parametric data. Binary logistic regression analysis was performed in the determination of the risk factors in CTEPH development. Multivariable conditional logistic regression analysis of the prognostic factors with a < 1 significance in univariable analysis was carried out by using stepwise descending method.

RESULTS

Three-hundred and eighteen patients with a diagnosis of PTE were included into the study. Thirty-two patients were excluded from the study due to exitus (7 acute PTEs, 20 PTEs + Malignancy, 5 PTEs + comorbidity), 100 patients were excluded since they did not come to their sixth month follow-up and 74 patients were excluded due to the fact that they had additional diseases that could cause pulmonary hypertension (21 COPDs, 46 HYs and/or CHDs, 3 COPDs + HF, 2 congenital heart diseases, one interstitial lung disease, one kyphoscoliosis). The remaining 112 patients were included into the study.

Mean age of the 112 patients included into the study was 57.09 ± 17.30 years (range, 16-86) and 57 were female. Fifty-four of the patients were started on unfractionated heparin (UFH) and 58 of them were started on low molecular weight heparin (LMWH) as first line treatment. As on-treatment, 81 patients were given oral anticoagulant (warfarin) and 31 patients were given DMAHorder. On-treatment of the patients was arranged to last 6 months in 69 of them, 3 months in 39 and lifetime in 4. CTEPH was detected in 52 of the 112 patients with PTE. Since 7 of these 52 patients with CTEPH had a previous history of PTE and DVT, these patients were excluded from the calculation of incidence. These patients were included into the study when other data were evaluated and risk factors were determined. PHT was detected by echocardiographic examination performed in the sixth month follow-up in 45 (8 symptomatics) of the 112 patients followed with a diagnosis of acute PTE. CTEPH incidence (symptomatic + asymptomatic) was determined as 40.16%. Only 8 of the CTEPH patients described symptoms, and hence, symptomatic CTEPH incidence was calculated as 7.14%. Thromboendarterectomy was performed on two of the eight patients with symptomatic

CTEPH, and six patients were started on medical therapy (iloprost for three patients, bosentan for 3 patients).

When patients with CTEPH and without CTEPH were compared, it was detected that the mean age was higher in patients with CTEPH (p= 0.02); whereas, there was no significant difference between the two groups in terms of gender and the presence of risk factors (p> 0.05 for all) (Table 1).

The presence of comorbidities was detected in 69 of the patients with CTEPH. The distribution of comorbidities in patients with and without CTEPH is presented in Table 2 and Table 3.

When the arterial blood gas findings of the patients during first admission were evaluated, PaO_2 and SaO_2 values in patients with CTEPH were significantly low when compared to the patients without CTEPH (p= 0.012, p= 0.057, respectively) (Table 4).

When the ECHO findings of the patients were assessed, it was determined that initial and 6th month PAB values of the patients with CTEPH were prominently higher than those of the patients without CTEPH (p= 0.001, p=< 0.001, respectively). When the thoracic CT scans of all patients with PTE were evaluated as regards the location of thrombus, it was detected that the localization of the thrombus was similar in both groups. It was also detected that the routinely evaluated D-dimer and troponin levels of the patients with PTE did not show a statistically significant difference (Table 5).

When the cases included into the study were assessed with univariate logistic regression analysis in terms of risk factors that could play a role in the development of CTEPH, it was found that the male gender (OR; 4.59, 95% CI; 1.071-19.683, p= 0.040), previous DVT existence (OR; 218, 95% CI; 1.235-38543.073, p= 0.041) and PaO_2 value < 80 mmHg (OR; 56.903, 95% CI; 2.656-1219.228, p= 0.010) were independent risk factors of CTEPH development (Table 6).

DISCUSSION

In this study where we investigated the developmental incidence of CTEPH in patients with acute pulmonary thromboembolism, we designated the number of patients, whose sPAB value was > 35 mmHg on the 6th month ECHO, as 45 (40.16%). We also detected that the male gender, previous DVT history and hypoxemia presence during diagnosis were independent risk factors.

Table 1. Demographic characteristics of the patients and risk factors

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
Age	62.46 ± 15.66	52.45 ± 17.44	**0.02***
Gender (M/F)	30/22	25/35	> 0.05
Idiopathic	34	35	> 0.05
Acquired risk factor	15	24	> 0.05
Congenital risk factor	3	1	> 0.05
Previous DVT history	3	5	> 0.05
Previous PTE history	5	1	> 0.05
Presence of Accompanying DVT	20	18	> 0.05

CTEPH: Chronic thromboembolic pulmonary hypertension. DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism.
* Statistically significant.

Table 2. Detected comorbidities in patients that developed CTEPH

Benign prostate hypertrophy	5 (7.24%)
Hypertension	31 (44.9%)
Diabetes mellitus	12 (17.39%)
Malignancy	6 (8.69%)
Hyperthyroid	2 (2.89%)
Chronic kidney failure	2 (2.89%)
Obesity	2 (2.89%)
Cerebrovascular disease	3 (4.34%)
Pnemonia	3 (4.34%)
Systemic lupus erythematosis	1 (1.44%)
Asthma	2 (2.89%)

CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 3. Detected comorbidities in patients that did not develop CTEPH

Hypertension	40 (59.70%)
Diabetes mellitus	10 (14.92%)
Malignancy	1 (1.49%)
Chronic liver failure	4 (5.97%)
Obesity	6 (8.95%)
Cerebrovascular disease	5 (7.46%)
Pnemonia	3 (4.47%)
Asthma	4 (5.97%)

CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 4. Arterial blood gas findings of the patients

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
pH	7.46 ± 0.06	7.44 ± 0.06	0.31
PaO_2 (mmHg)	56.30 ± 15.84	63.81 ± 15.03	**0.012***
SaO_2 (%)	84.73 ± 12.63	89.40 ± 13.02	**0.057***
$PaCO_2$ (mmHg)	32.68 ± 6.03	32.78 ± 6.38	0.93
HCO_3 (mEq/L)	21.96 ± 3.80	22.76 ± 3.42	0.24

CTEPH: Chronic thromboembolic pulmonary hypertension.
* Statistically significant.

Table 5. ECHO and CT findings of the patients and D-Dimer, troponin levels

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
PAB basal	56.46 ± 22.01	44.15 ± 13.59	**0.001***
PAB 6th month	51.51 ± 21.44	31.45 ± 3.11	**0.000***
Thrombus localization			
Major pulmonary artery	28	33	> 0.05
Lobar pulmonary artery	10	12	> 0.05
Segmenter pulmonary artey	14	15	> 0.05
D-Dimer	3.56 ± 1.64	4.13 ± 2.18	0.11
Troponin	0.21 ± 0.35	0.14 ± 0.24	0.25

CTEPH: Chronic thromboembolic pulmonary hypertension. CT: Computed tomography, PAB: Pulmonary artery pressure.
* Statistically significant.

Table 6. Independent risk factors in the development of CTEPH

Covariate	b	SE	P	Exp (b)	95% CI of Exp (b)
Gender	-0.6183	0.3498	0.07717	0.5389	0.2724 to 1.0660
PaO_2	-0.7516	0.5548	0.1755	0.4716	0.1599 to 1.3914
Previous DVT	-0.8658	0.7616	0.2556	0.4207	0.0953 to 1.8576

CTEPH: Chronic thromboembolic pulmonary hypertension, DVT: Deep vein thrombosis.

It has been previously thought that there was a 'honeymoon phase' between the clinical findings of CTEPH and acute PTE and that the clinical findings of CTEPH would manifest themselves many years later [11]. It is recommended by the guidelines that patients, in whom findings of PHT or right ventricule dysfunction is detected during hospitalization due to acute PTE, should undergo a follow-up echocardiography after discharge (usually 3-6 months later) in order to determine if PHT has improved [9]. In our study, CTEPH development was detected 6 months after the acute event and these cases were found to have a high sPAB value within a mean follow-up period of 21.2 months (6-60 months).

It has been previously believed that the developmental incidence of CTEPH after acute PTE was between 0.1% and 0.5% [12,13]. Further studies have detected that this rate is much higher. In a prospective study by Martive et al., it has been detected that the incidence of CTEPH is 9.0% [14]. In another more recent study, CTEPH incidence of 94 patients, whose mean follow-up period was 25.47 months (4-62 months), has been found as 14.4% [15]. In a study by Pengo et al., the incidence of symptomatic CTEPH in the follow-up of their 223 patients has been found as 1.0% 6 months later, 3.1% one year later and 3.8% 2 years later [6]. In a study carried out in our country, it has been reported that the incidence of symptomatic CTEPH during a mean follow-up period of 16.3 months was 4.6% and that CTEPH developed within a year after the acute event in most of the patients (80%). It has been indicated in the same study that diagnosis could be made in patients with symptomatic CTEPH in a mean 9.4 months. The researchers have stated that CTEPH manifested clinical symptoms especially within the first 1 year and presented a quiet picture in later years [16]. When the incidence of CTEPH detected in our study was compared to the literature, it was seen that the incidence detected in our study was prominently higher. When the reason for it was researched, we detected that the incidence of CTEPH was mostly given by including symptomatic patients. When we grouped our patients as symptomatic/asymptomatic, we saw that the incidence of symptomatic CTEPH was 7.14%.

Risk factors having a part in the development of CTEPH are multifold. One of these factors is the presence of residual thrombus. It is known that full thrombus resolution and full improvement in the pulmonary vascular bed occur in the 4^{th}-8^{th} [9]. weeks. It has been reported that there was full resolution after 4 weeks in 81% of the 69 patients with PTE, who were followed by CT angiography [17]. However, it has been detected in studies that full resolution is seen within this period of time in only 50% and 80% of the cases [17,18]. Residual perfusion defect has been established in 66% of 157 PTE patients whose perfusion sscintigraphy was performed after a 3-month anticoagulant treatment [19]. In another study, residual perfusion defect has been confirmed in 29% of 254 PTE patients one year after diagnosis [20]. Residual chronic thrombus develops in many PTE patients; however, new studies need to be carried out in order to determine the clinical importance of this finding in the long term [21]. In this study where we included 112 PTE patients, we confirmed the presence of chronic thrombus in 13 patients (11.6%) in the 6^{th} month. Out of these, 7 patients were in the symptomatic CTEPH group, 5 patients in the asymptomatic CTEPH group and one patient in the group where CTEPH did not develop. We determined in our study that the presence of residual thrombus in the 6^{th} month was not a risk factor for the development of CTEPH.

It is known that recurrent thromboembolisms play a role in the development of CTEPH [22]. In a retrospective study by Bonderman et al., risk factors in CTEPH patients were investigated and splenectomy, previous venous thromboembolism, recurrent VTE, blood types apart from 0 and the presence of lupus anticoagulant/antiphospholipid anticores were determined to be associated with CTEPH [23]. In a study conducted in our country, the incidence of CTEPH was determined higher in cases with previous PTE and idiopathic PTE [16]. Again in a study by Pengo et al., CTEPH was confirmed in three (5.2%) of the 58 cases with a history of DVT [6]. We also established in our study that history of DVT was an independent risk factor in the development of CTEPH.

Advanced age is thought to be a risk factor in PTE development [24]. However, data stating that age is a risk factor for the development of CTEPH are conflicting. While advanced age has been defined a relative risk factor in a study [14], other studies have shown that young age is associated with the development of CTEPH [6,25]. There are studies reporting that age is not a risk factor for the development of CTEPH [16,26]. We established in our study that CTEPH patients were significantly older than the patients without CTEPH: however, we also confirmed with regression analyses that age was not effective in the development of CTEPH.

The number of studies where gender has been investigated as a risk factor is limited. Female gender has been determined a risk factor in a study [23]. In our study, it was established that male gender increased the risk of development of CTEPH 4.59 times.

Different results have been obtained in studies investigating the correlation between CTEPH development and thrombus

localization. Korkmaz et al. have reported in their study that much thrombus load and CTEPH development have a significant relation; however, a significant relation has not been not reported between the localization of thrombus and CTEPH development [16]. In earlier studies, wide perfusion defects have been reported as risk factors in the development of CTEPH [6,27]. In our study, a correlation between the localization of thrombus and CTEPH development was not confirmed.

Increased PAB and right ventricular dysfunction are seen in nearly half of the PTE cases, which is also associated with early period mortality [26]. In a study conducted in our country, right ventricular dysfunction and high sPAB (> 35 mmHg) have been confirmed in 57% of acute PTE patients. In the same study, it has been confirmed that sPAB is higher in patients with CTEPH when compared to the ones without CTEPH [16]. In a study by Lang et al., it has been reported that high basal sPAB value is a risk factor for CTEPH [24]. In another study, high basal sPAB value, recurrent PTE, increased right atrium and ventricular diameter have been defined as high risk factors for the development of CTEPH [15]. Situations where PAB value is measured during an acute PTE and is higher than 50 mmHg have been found associated with persistent PHT development in the late period [27]. During acute PTE in our study, right ventricular dysfunction and high sPAP (50 mmHg and over) were detected in 35.7% of our patients. Basal sPAB values were determined to be significantly higher in cases with CTEPH when compared to the cases without CTEPH. Basal sPAB was detected high especially in all symptomatic CTEPH patients. However, high value of sPAB was not detected a risk factor in the development of CTEPH.

Hypoxemia is a vital clinical finding of PTE. Mechanisms playing role in the development of hypoxemia are V/Q imbalance, diffusion defect and intrapulmonary shaft development. Hypoxemia contributes to the development of PHT by increasing PVR. In our study, we confirmed that PaO_2 and SaO_2 values were prominently low in patients with CTEPH when compared to the patients without CTEPH.

One of the limitations to our study is that PAB was evaluated with ECHO rather than pulmonary aretry catheterization. However, in ESC/ERS/ISHLT guidelines, an important correlation has been shown between the PAP value of 50 mmHg and higher on ECHO and the sPAP value of 50 mmHg and higher during pulmonary artery catheterization [9]. Another limitation to our study is that the number of patients that could not be followed was high. We do not know the number of symptomatic patients among the unfollowed cases. Another limitation is that cases with a disease causing PHT were excluded from the study since PHT does not develop in all of these disease, CTEPH that develop in these patients are overlooked or attributed to an additional disease.

In conclusion, CTEPH development after PTE occurs in rate close to 50%. Close monitoring of PTE and the appropriate length of use of anticoagulant therapy are vital to prevent the development of embolism and CTEPH.

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ORIGINAL INVESTIGATION

Use of High-Resolution Computed Tomography (HRCT) in Diagnosis of Sputum Negative Pulmonary Tuberculosis

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Abstract

OBJECTIVES: To study the role of high-resolution computed tomography (HRCT) in the diagnosis of pulmonary tuberculosis (PTB) in sputum smear negative patients and to design HRCT criterion to forecast the threat of pulmonary tuberculosis.

MATERIAL AND METHODS: We studied 69 patients having sputum smear negative for acid-fast bacilli (AFB) but still with clinical suspicion of PTB after taking written informed consent. We studied their medical characteristics, numerous separate HRCT-results and combination of HRCT findings to foresee the danger for PTB by utilizing univariate and multivariate investigation. Temporary HRCT diagnostic criteria were planned in view of these outcomes to find out the risk of PTB and tested these criteria on our patients.

RESULTS: Chronic cough and night sweats were highly linked to a greater risk of PTB among clinical features. On HRCT chest presence of cavity, centrilobular nodules, consolidation, ground glass opacity (GGO), lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation, other minute nodules and tree in bud appearance was significantly linked to an elevated risk of PTB in linear regression analysis. While cavity, centrilobular nodules, interlobular septal thickening, pleural effusion and tree-in-bud appearance was significantly linked to a greater threat of PTB in multivariate regression analysis. Positioning of the patients utilizing our HRCT indicative criteria uncovered reliable sensitivity and specificity for PTB patients determining that HRCT is a useful tool in sputum negative PTB patients.

CONCLUSION: HRCT is useful in selecting individuals with greater chances of PTB in the sputum smear-negative setting.

KEYWORDS: Tuberculosis pulmonary, tomography, sputum

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INTRODUCTION

Tuberculosis is one of the oldest ailments having an impact on humankind, and is a noteworthy reason for mortality around the world. Causative agent of tuberculosis is *Mycobacterium tuberculosis* complex, and mostly influences the lungs. Other organs are affected in up to 33% of cases. Drug susceptible tuberculosis is curable in essentially all cases. In the event that it is left untreated, the malady may be deadly within a timespan of 5 years in 50-65% of cases [1]. Prevalence of tuberculosis in India was 2.6 million in 2013 [2]. The successful treatment of pulmonary tuberculosis (PTB) involves making an accurate diagnosis and starting timely anti-tuberculosis medications. In clinical practice, tuberculosis (TB) is treated based on patient symptoms, chest radiography (CXR) abnormalities and sputum bacteriological examination. Sputum smear test can find acid-fast bacilli (AFB) in almost 50-60% of cases of pulmonary tuberculosis [3]. Sadly, in some cases of current active pulmonary TB, neither bacteriological examination nor serial CXR unequivocally demonstrates the activity of disease. Such Patients (smear-negative TB patients) are although at a lesser risk of spreading the disease than the smear-positive patients, but still able to transmit the disease or infection. The relative transmission rate of smear-negative TB patients in contrast to smear-positive TB patients has been ascertained at 22% utilizing a molecular epidemiologic method [4]. A large portion of all patients (almost 50%) with TB can have negative sputum smear results, as a result of which the total contribution of smear-negative TB patients to the transmission of the disease is notable. Polymerase chain response (PCR) can quickly analyze sputum samples, however sensitivity is low [5]. As a result, clinicians often hesitate in starting anti-tuberculosis treatment for fear of the

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potential side-effects of anti-tuberculosis drugs. Then again, to confine the cost and potential hazards of empiric treatment correct identification of individualswho are unlikely to have TB is important as well. High Resolution Computed Tomography (HRCT) has been discovered to be more sensitive than chest x-ray in the identification of small exudative lesions, slight or occult parenchymal disease and in assessing disease activity in pulmonary TB. Moreover, sputum culture reports in sputum smear negative patients takes upto 6 to 8 weeks posing a clinical dilemma of whether to treat or not. Liquid culture methods and nucleic acid amplication methods like GeneXpert MTB/RIF (*Mycobacterium tuberculosis*/resistance to rifampicin) assay are costly and not widely available yet. In such situations, HRCT can help in providing provisional diagnosis of tuberculosis so that empirical therapy may be started and on the other hand selecting patients unlikely to have tuberculosis.

In this study, we investigated the function of a high resolution computed tomography (HRCT) scan of the thorax in the analysis of PTB in sputum smear-negative patients. We also designed criteria based on a mixture of HRCT findings to determine the threat of pulmonary tuberculosis.

MATERIAL AND METHODS

A protocol for study was constructed and approval taken from ethical board of our establishment. Permission in writing was taken from all patients. We studied 69 patients over a period of one year from June 2013 to May 2014 with suspicion of pulmonary tuberculosis taking into account the vicinity of one or a greater amount of the following symptoms: cough of at least 2 weeks or more; hemoptysis, constitutional symptoms such as loss of weight, fever, or night sweating with chest radiograph suggestive of tuberculosis. All patients had two consecutive sputum smears negative for acid fast bacilli (AFB) or they were unable to produce sputum after multiple attempts. The sputum samples were collected as per Revised National Tuberculosis control Program (RNTCP) norm and all sputum samples were sent for direct smear examination using Zeihl-Neelsen Stain. We excluded the patients who were sputum smear positive, pediatric patients and patients with only extra-pulmonary involvement.

Brief history was recorded including cough, hemoptysis, fever, decrease in weight, night sweats and time period of symptoms. Chest X-ray was performed followed by HRCT on 64 slice MDCT GE (General Electronics) LIGHT SPEED VCT Xte machine. Patient was said to have active pulmonary tuberculosis based on the presence of TB bacilli in bronchial washings/ broncho-alveolar lavage (BAL), cultures of sputum or bronchial washings/BAL, demonstration of non-caseating granuloma on FNAC or TBLB suggestive of TB or radiographic and clinical improvement after administration of anti-tubercular drugs for patients whose clinical and radiographic findings suggested a diagnosis of pulmonary tuberculosis. At least two experts from the Department of Radio-Diagnosis of our institute analysed the images obtained independently and any difference of opinions was solved by consensus.

We examined the accompanying HRCT discoveries: centrilobular nodules, other minute nodules, huge nodules, masses, fine granular pattern, lobular distribution of consolidation, interlobular septal thickening, consolidation, ground-glass opacities, cavitation, branching linear opacities, tree-in-bud appearance, bronchiectasis, pleural effusion, lymphadenopathy and the vicinity of a main lesion in bilateral upper lobes.

These findings were defined as follows. Centrilobular nodules and other nodules: the small nodules of < 8 mm were differentiated into centrilobular noduless and other nodules, that are interstitially or arbitrarily spread out. Huge Nodules: Nodules of ≥ 8 mm and < 30 mm were viewed as large nodules. Mass: A nodule of ≥ 30 mm was viewed as a mass. Fine granular pattern: fine nodular opacities connected with vessels or lymphatic lesions were viewed as a fine granular pattern. Lobular distribution of consolidation: Areas of consolidation outlined by sharp edges relating to 1 or 2 lobules. Regression analysis was used to find the blend of HRCT findings that foresee the threat of PTB. In view of these outcomes, a mix of HRCT findings was selected and positions were given based on these results to determine the threat for pulmonary tuberculosis as position 1, 2, 3 and 4. Specificity, sensitivity, positive likelihood ratio and negative likelihood ratio of distinctive positions were computed.

Statistical Analysis

The information collected was evaluated and studied further with SPSS statistical software version 20. Data are expressed in terms of means ± standard deviation. $p< 0.05$ shows a significant relationship. Regression analysis was used to determine the clinical components and HRCT discoveries linked or associated with the danger of PTB. Positive predictive values, negative predictive values, sensitivity and specificity were computed wherever relevant.

RESULTS

Analytical and Medical Characteristics

Age of participants varied between 18 to 85 years in our study. The average age was 35.7 ± 16.9 years. Out of 69 patients there were 38 men and 31 women. Forty one patients were found to have pulmonary tuberculosis. Among the 41 patients found to have tuberculosis, 18 were men and 23 were women. The average age of individuals affected by pulmonary tuberculosis was 31.5 ± 15.4 years. Twenty eight patients were found to have disease other than pulmonary tuberculosis. Among clinical findings chronic cough and night sweats were significantly linked to a greater possibility for PTB (Table 1).

HRCT Findings

On HRCT thorax, presence of cavity, lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation, other minute nodules and tree in bud appearance centrilobular nodules, consolidation, ground glass opacity (GGO), was linked to higher chances of PTB in linear regression analysis significantly (Table 2). While cavity, pleural effusion, centrilobular nodules, interlobular septal thickening and tree-in-bud appearance was significantly linked or associated with a higher possibility of PTB in Multivariate regression analysis (Table 3). Positions were given from 1 to 4 according to HRCT findings (Table 4). Positive predictive value, negative predictive value, sensitivity and specificity were ascertained. When position 1 (Figures 1A,1B) alone was taken to be positive; negative predictive value, sensitivity and

Table 1. Multivariate regression analysis of demographic and clinical findings of sputum smear-negative PTB and Non-PTB patients

	PTB	Non-PTB	Coefficient	p-value
Age (years)	31.5	41.7	0.002	0.67
Cough	38	16	0.776	0.01
Chronicity of cough (duration, days)	31.1	37.4	0.013	0.02
Hemoptysis	5	12	-0.368	0.02
Fever	33	21	0.061	0.68
Male gender	18/41	20/28	-0.162	0.16

PTB: Pulmonary tuberculosis.

Table 2. Linear regression analysis of HRCT lesions

Variable	p-value
Centrilobular nodules	0.00
Other minute nodules	0.00
Huge nodules	0.37
Fine reticular pattern	0.33
Branching linear opacity	0.57
Tree-in-bud appearance	0.00
Lobular pattern of consolidation	0.00
Interlobular septal thickening	0.24
Consolidation	0.04
Ground-glass opacity	0.00
Cavity	0.00
Bronchiectasis	0.93
Pleural effusion	0.69
LAP	0.00
Main lesion in S1, S2 or S6	0.00

HRCT: High-resolution computed tomography.

specificity were 0.43, 53.6% and 100% respectively. When ≤ position 2 (Figures 2A, 2B) was taken to be positive; positive predictive value, negative predictive value, sensitivity and specificity were 23.22, 0.18, 82.9% and 96.43% respectively. When ≤ position 3 (Figures 3A,3B) was considered positive, these values were 1.56, 0, 100% and 35.7%, respectively (Table 5). The sensitivity and specificity of HRCT in sputum smear negative PTB patients in our research was 82.7% and 96.4% respectively.

DISCUSSION

Visualization of *M. tuberculosis* in sputum smear microscopy, culture of mycobacterium tuberculosis using solid or liquid culture media followed by drug susceptibility testing are considered standard for diagnosis of pulmonary tuberculosis [6]. Sputum smear examination can distinguish acid-fast bacilli (AFB) in up to 50-60% of instances of pulmonary tuberculosis. The rates of AFB detection are further lower in low-income economies due to lack of access to top notch microscopy services. Due to paucibacillary tubercular disease in HIV patients, the issue of the low sensitivity of smear examination is exaggerated further in nations with high pervasiveness of HIV/AIDS [3]. Delayed diagnosis can

Table 3. Multivariate variable regression analysis of HRCT lesions in sputum smear-negative PTB and Non-PTB

	PTB		Non-PTB		
	Number	Percentage	Number	Percentage	P value
Centrilobular nodules	35	85.4	5	17.8	0.00
Other minute nodules	35	85.4	14	50	0.43
Huge nodules	16	39	8	28.6	0.15
Fine reticular pattern	4	9.7	1	3.6	0.86
Branching linear opacity	4	9.7	4	14.3	0.61
Tree-in-bud appearance	27	65.8	0	0	0.01
Lobular pattern of consolidation	29	70.7	10	35.7	0.06
Interlobular septal thickening	2	4.9	0	0	0.00
Consolidation	26	63.4	11	39.3	0.51
Ground-glass opacity	33	80.5	12	42.8	0.11
Cavity	30	73.2	4	14.3	0.00
Bronchiectasis	7	17	5	17.8	0.71
Pleural effusion	2	4.9	2	7.1	0.00
LAP	41	100	23	82.1	0.07
Main lesion in S1, S2, S6	30	73.2	5	17.8	0.46

HRCT: High-resolution compudet tomography, PTB: Pulmonary tuberculosis.

Table 4. HRCT diagnostic criteria for diagnosing sputum smear-negative PTB

Position	HRCT diagnostic criteria	Findings
1.	Highly suspected PTB	Presence of at least 3 of the following findings: main lesion in upper lobes, apical lobes of lower lobes; tree-in-bud appearance; lobular consolidation; nodules (large or centrilobular).
2.	Probable PTB	Presence of at least 2 of the following findings: main lesion in upper lobes, apical lobes of lower lobes; tree-in-bud appearance; lobular consolidation; nodules (large or centrilobular)
3.	Nonspecific or difficult to differentiate from other diseases	No characteristic findings indicating other diseases or findings that are difficult to differentiate from other diseases.
4.	Other suspected diseases	Some findings indicating other specific diseases.

HRCT: High-resolution compudet tomography, PTB: Pulmonary tuberculosis.

Table 5. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for each rank of HRCT diagnosis

	≤ Rank 3	≤ Rank 2	Rank 1
Sensitivity	100%	82.9%	53.6%
Specificity	35.7%	96.4%	100%
Positive likelihood ratio	1.56	23.22	-
Negative likelihood ratio	0	0.18	0.43

HRCT: High-resolution compudet tomography.

lead to the spread of infection in the society. Clinicians often face the difficulty of adding empirical treatment or waiting for up to 8 weeks for the culture results. Liquid media based culture methods like MGIT (Mycobacterial growth indicator tube) can provide culture reports as early as 2-3 weeks but at relatively high costs [7]. Disadvantages of culture methods are high degree of technical expertise required, high cost, non uniform availability and time required to obtain a result causing diagnostic delay. GeneXpert MTB/RIF assay is a nucleic acid amplication assay. It can provide results in less than two hours and can determine rifampicin resistance at the same time. Sensitivity of GeneXpert MTB/RIF assay in smear negative setting is 72.5% and specificity is 99.2% in diagnosis of pulmonary tuberculosis. But again it is expensive and not available in resource poor settings [8]. In spite of the fact that newer less time consuming analytic tests are accessible, they are expensive and yet are not considered standard of practice. In this research, we tried to determine the role of HRCT in sputum smear-negative PTB patients for early diagnosis and treatment of such patients. The average age of the individuals affected with pulmonary tuberculosis was 31.5 ± 15.4 years in our study which was slightly less as compared to other similar studies [5,6].

The younger mean age in our study could be explained by the fact that ours being developing country has much higher

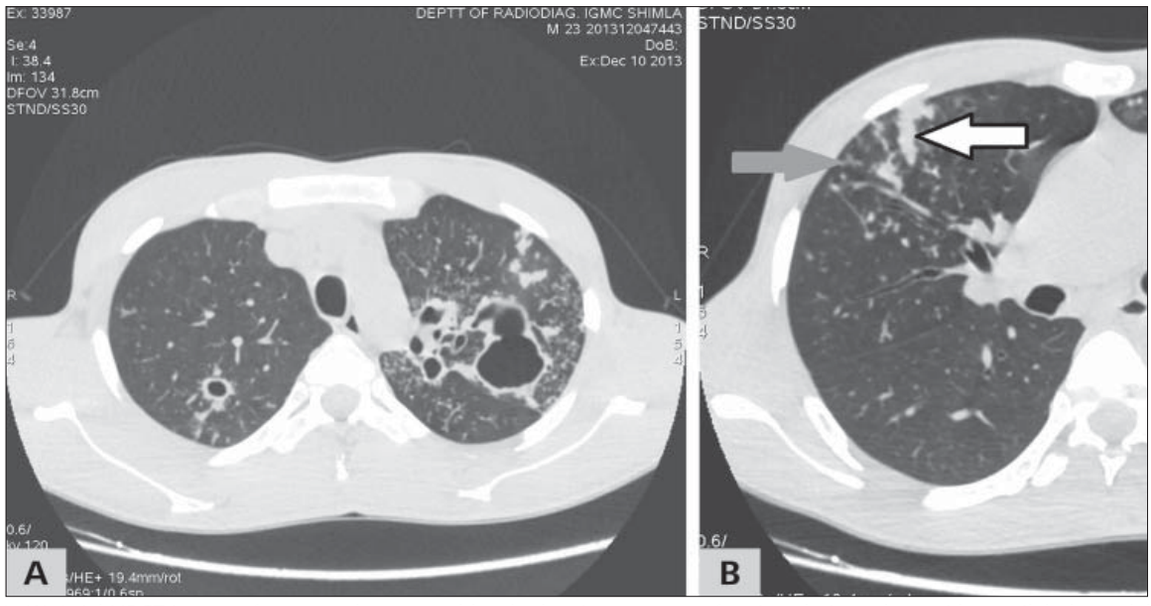

Figure 1. (A) Axial HRCT images of a twenty three year old male showing presence of cavitary lesions along with centrilobular nodules and consolidation in lobular pattern in the surrounding lung parenchyma in b/l upper lobes. **(B)** Magnified view of the same patient showing the centrilobular nodules, tree-in-bud appearance (dark arrow) and consolidation in lobular pattern (white arrow).This patient was given Rank 1 and proved to be tubercular on BAL examination.

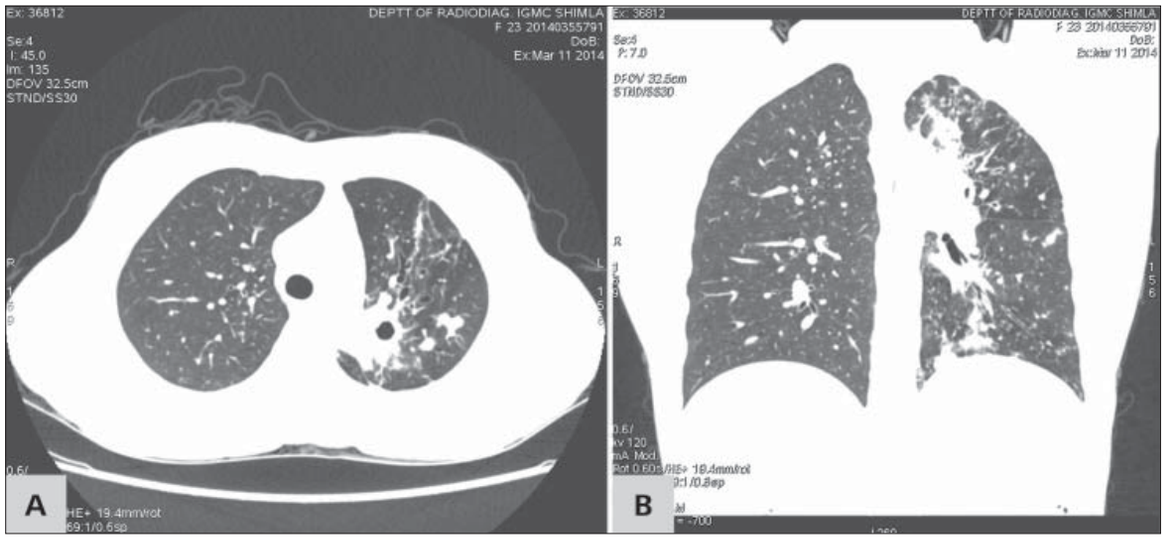

Figure 2. (A) Axial sections showing cavity, nodules and few centrilobular infiltrates with traction bronchiectasis in left upper lobe (anterior and apical segments). **(B)** Coronal sections showing the upper lobe distribution of main lesions. This patient was given Rank 2 and was proved tubercular on microbiological analysis.

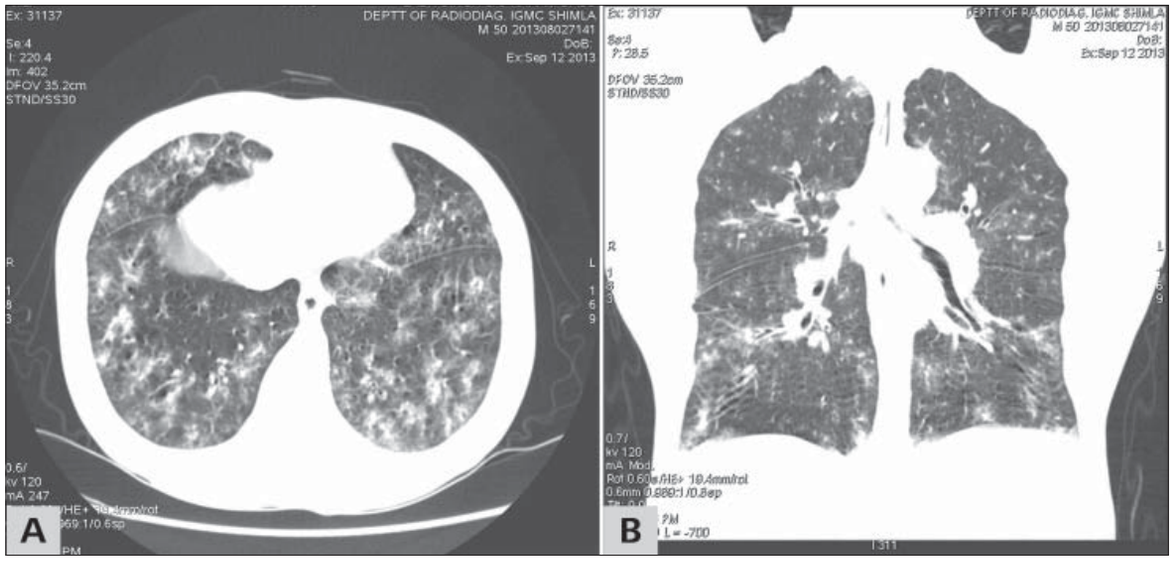

Figure 3. (A) Axial sections of HRCT chest of a fifty year old male patient showing diffuse patches of consolidation and surrounding ground glass haze, no specific apicobasal gradient seen. **(B)** Coronal sections also showing diffuse patches of consolidation and surrounding ground glass haze. This patient was given Rank 3. He responded to symptomatic treatment and recovered in 2 weeks.

exposure rate of tuberculosis and so TB occurs at a younger age as compared to the developed countries. Age and gender were not significantly associated with risk of tuberculosis. Among clinical features cough was the most common presenting complaint in our patients followed by fever, while chronic cough and night sweats were significantly associated with risk of pulmonary tuberculosis. A negative correlation was demonstrated with symptoms of hemoptysis i.e. hemoptysis was seen more in patients who were diagnosed non-tubercular. Out of the 17 patients with hemoptysis only 5 had tuberculosis and 12 patients were non-tubercular. A clarification for this result may be that moderately less quantity of bacilli in smear negative patients are not able to cause the pathological changes required to produce hemoptysis.

Tree in bud appearance, cavity, centrilobular nodules, consolidation, ground glass opacity (GGO), lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation and other minute nodules were significantly linked with pulmonary tuberculosis on regression analysis. Causes of tree-in-bud appearance are respiratory infections with mycobacteria, bacteria or viruses, cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), aspiration, and graft versus host disease. Tree-in-bud opacities arise from extensive bronchiolar mucoid impaction in the presence or absence of additional involvement of adjacent alveoli. Infectious bronchiolitis is the most significant differential diagnosis for this behavious of disease [10]. The specificity and sensitivity of this finding was 100% and 57% respectively in some previous studies [11]. In our study the specificity of this finding was 100% and the sensitivity was 65.8%. Centrilobular nodules can be found in hypersensitivity pneumonitis, respiratory bronchiolitis, immunodeficiency, mineral dust airway disease, pulmonary

Langerhans cell histiocytosis, respiratory bronchiolitis-interstitial lung disease, connective tissue disease (Sjögren syndrome, rheumatoid arthritis), and pulmonary infections. Specificity and sensitivity of centrilobular nodules were found to be 93% and 100% respectively in previous studies [10]. The sensitivity and specificity of centrilobular nodules was found to be 82% and 82.4% respectively in our study. Cavity can be found in tuberculosis, non-tuberculous mycobacterial infection, aspergillosis, lung abscess, wegener's granulomatoses, and metastatic neoplasm [12]. The sensitivity of the cavitatory lesions was 73% and the specificity was 85.7% in our study. Although individual findings are non-specific for diagnosis of tuberculosis, combination of HRCT findings can be helpful.

Positions were given based on combination of HRCT findings from 1 to 4 predicting the risk of tuberculosis. Position 1 was given to 22 patients (53.6%) and all of them were found to have pulmonary tuberculosis. Position 4 was found in 9 (32.1%) patients and all of them were found to have disease other than pulmonary tuberculosis. Thus patients with position 1 are more likely to have pulmonary tuberculosis and extensive work up for pulmonary tuberculosis can be undertaken in these patients.

We postulated that HRCT scan could not only diagnose PTB but also could exclude patients not having PTB. In our study the sensitivity and specificity of HRCT in sputum smear-negative PTB patients was 82.7%, and 96.4% respectively. The high specificity demonstrated in our study could be due to the high prevalence of tuberculosis in our set-up and the low sensitivity and specificity of the smear examination producing false-negative results. Also, the HRCT criteria takes into account a mixture of HRCT findings which becomes sufficiently reliable to anticipate the risk of PTB and could help isolate the patients highly suspected of having PTB.

Limitations

Utilization of HRCT to analyze PTB is not accessible at each center especially in developing countries. Immunocompromised patients were not evaluated in our study. The pathological response of pulmonary tissues to *Mycobacterium* could be altered in immunocompromised patients and simultaneous presence of other lung diseases in immunocompromised patients could interfere with diagnosis [13,14]. In this manner, the certainty of HRCT diagnosis for such patients stays ambiguous.

Conclusion

The main use of HRCT for diagnosing PTB in sputum smear negative patients is that the patient highly suspected for PTB can be selected among patients based on combination of characteristic HRCT findings. Thus it helps in selecting the patients for further invasive or advanced investigations besides excluding other diseases that can clinically mimic PTB.

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ORIGINAL INVESTIGATION

Respiratory Disability in The Van Region Based on the Medical Board Reports

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Abstract

OBJECTIVES: Respiratory system disorders have an impact on daily living activities of subjects, resulting in disability. Data should be gathered on disability for health services. The present study aimed to review the records of patients with a respiratory disability report from our medical board, and contribute to the national and regional statistics on disability.

MATERIAL AND METHODS: We retrospectively reviewed sociodemographic characteristics, respiratory diseases and disability rates of the patients who were examined by the Chest Diseases Department during the Medical Board evaluations in our hospital between January 1st and July 1st, 2014.

RESULTS: Among 4285 patients whose applications were submitted to the medical board for evaluation, 401 (9.3%) had a respiratory disease. Of these patients, 163 were male, and 238 were female, with a mean age of 64.2 years. The most common diseases associated with disability were chronic obstructive pulmonary disease, asthma and sequelae tuberculosis.The disability rating for respiratory system was 80% in 24.9% of patients, 40% in 34.7% of patients, and 20% in 40.4% of patients. Patients with a respiratory disability report were also considered disabled by the departments of Physical Therapy and Rehabilitation, Cardiology and Eye diseases. There was a positive correlation between disability rating and age, and a negative correlation between forced expiratory volume in first second (FEV_1) and oxigen saturation measured by pulse oximeter (SpO_2) values ($p= 0.002$; $p< 0.001$; $p< 0.001$, respectively). Furthermore, smokers had a higher disability rating compared to non-smokers ($p= 0.02$).

CONCLUSION: In Turkey, we have limited number of studies about respiratory disability. We believe that the present study will help determination of the etiology of respiratory disability and contribute to any action on prevention of these disorders in our region.

KEYWORDS: Lung diseases, disability evaluation, spirometry.

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INTRODUCTION

Disability is referred to as having difficulty in meeting daily requirements and adapting to the social life, and requiring protection, care or rehabilitation, counseling and support services due to impairment of physical, cognitive, psychological, sensory and social functions at various extents. It may be congenital or acquired [1,2]. It may be temporary or permanent [3].

A disabled person requires a Medical Board report indicating disability rating in order to benefit from protection, care or rehabilitation, counseling and support services within the framework of definition of disability [1] .

However, assessment of disability status presents as an issue with various medical, legal and social aspects. Data on this subject have been added to the agenda with occupational diseases at the beginning of the 20th century worldwide [4]. In Turkey, procedures for assessment of people with disability started in 1946 with evaluations on pneumoconiosis, and the law enacted in 1964 indicated that people would be able to benefit from some rights such as financial aid, disability indemnity and/or early retirement due to work accident and occupational disease, disability, senility andindigence [4]. "The Regulation on the Criteria and Classification of Disability and the Medical Board Reports to Be Issued for Disabled People" published in the official gazette with number 28.173 dated 14.01.2012 represents the most recent legal arrangement made regarding the subject [1] .

The Turkish Thoracic Society has designed a guideline to help chest disease specialists make a decision on any potential problems in determining respiratory disability based on medical data [4]. A protocol for assesment of respiratory disability according to these guidelines has been provided in (Table 1).

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Table 1. According to the degree of disability affected the overall respiratory disability

	Category 1 No loss of function **Disability rate 0%**	**Category 2** Mild functional loss **Disability rate 10-15%**	**Category 3** Moderate functional loss **Disability rate 30-45%**	**Category 4** Severe functional loss **Disability rate 50-100%**
FVC (%)	≥ 80%**	60-79%	51-59%	< 50%
FEV_1 (%)	≥ 80%**	60-79%	41-51%	< 40%
FEV_1/FVC	≥ 75%	60-74%	41-59%	< 40%
DLCO (%)	≥ 80%**	60-79%	41-59%	< 40%
or	or	or	or	or
VO_2 max (mL/kg/min)	≥ 25 (mL/kg/min)	20-25 (mL/kg/min)	15-20 (mL/kg/min)	> 15 (mL/kg/min)
Expected (%)	> 70%	60-69%	40-59%	< 40%
(METS*)	> 7.1	5.7-7.1	4.3-5.7	< 4.3

* Metabolic equivalents.
** or ≥ the absolute value as the lower limit of normal.

The World Health Organization (WHO) indicates that the disabled people represent 10% of the population in developed countries, and 12% of the population in developing countries [3.5].

In 2002 a detailed survey by the Turkish Statistical Institute showed that the ratio of disabled people in Turkish population was 12.29%. Studies conducted in several cities of Turkey have shown a ratio ranging from 4.9% to 12.7% [5-8] . These studies examined general characteristics of disabled people. However, the number of studies examining patients with a disability report from the chest diseases department is very small [9].

The objective of the present study was to determine the extent of respiratory disability in patients who presented to medical board for assessment of disability, identify the incidence with concomittant diseases, contributing to the national health statistics and preventive medicine in order to avoid any disease associated with disability. Furthermore, we believe that the results of the present study will provide statistical information of the patients with a respiratory disability, guiding the planning of healthcare professionals in the field of respiratory system diseases.

MATERIAL AND METHODS

The present study retrospectively reviewed the reports of patients who presented for assessment of their disability by the Medical Board of the hospital between January 2014 and July 2014. A permission was obtained from the Ethics Committee for the paper. It included 401 patients with a respiratory disability report. We recorded the information on age, gender, residential address, occupational anamnesis, smoking, biomass exposure, respiratory symptoms, physical examination and radiological results of respiratory system, results of the respiratory function test, oxygen saturation results as measured by pulse oximeter and disability rating of patients as determined by the Chest Disease Department and other departments.

The Respiratory Function Test was performed by the same technician at least three times in seated position during a stable period of the patient by a spirometry after teaching forced vital capacity (FVC) maneuover. The reports included data on FVC, forced expiratory volume in 1 second (FEV_1), and the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC).

Oxygen saturation measured by pulse oximeter (PlusMed Pulse Oximeter Plus-50 DL, Made in P.R.C.), while patients rested and in a sitting position, on index finger.

The disability rating was determined according to the criteria clarified by the "Regulation on the Criteria and Classification of Disability and the Medical Board Reports to Be Issued for Disabled People" which was published in 1998 and updated in 2012 [1] .

The disability rating was recorded in the report as 20% if there was less impairment of respiratory and circulatory function, 40% if there was a moderate impairment of respiratory and circulatory function, and 80% if there was a severe impairment of respiratory and circulatory function or development of chronic cor pulmonale, and chronic type 2 respiratory failure.

Statistical Analysis

Descriptive statistics for the continuous variables were presented as Mean, Standard deviation, minimum and maximum values while count and percentages for categorical variables. One way ANOVA was used to compare group means. Duncan multiple comparison test was also used to identify different group means fallow ANOVA. For determination linear relationship among variables, Pearson correlation analysis was carried out. In addition, chi-square test was performed to determine the relationship between categorical variables. Statistical significance level was considered as 5% and SPSS (Statistical Package for Social Science, Chicago, IL, ABD) 19.0 statistical program was used for allstatistical computations.

RESULTS

A total of 4285 individuals presented to the Medical Board of our hospital during a 6-month period between January 2014 and July 2014, and 401 (9.3%)was identified as disabled at various degrees by the Chest Diseases Department. Of these patients, 49.6% were from the city center, 37.4% from the districts of Van, and neighboring cities including 3.5% from

Ağrı, 3% from Siirt, 2.5% from Hakkari, 2.5% from Bitlis, and 1.5% from Muş.

Of these patients with a disability report from the Chest Diseases Department, the mean age was 64.2 years. 59.4% were female, and 40.6% were male. The median age was 22, 43, 61, 80 for age groups 10-30, 31,50, 51,70, 71 and above sequentially.

The occupation of 40 (9.9%) patients was recorded as follows: housewife (30%), farmer (25%), industrial worker (17.5%), construction worker (15%), public servant (10%) and hairdresser (2.5%), respectively. Among those patients, 27.4% were smokers, and 29.7% had biomass exposure.

Lung auscultation showed rhonchi in 23.7%, cracles 16.7%, decreased respiratory sounds in 29.7% and prolongation of expirium in 12% of patients.

It was found that 325 (81.2%) patients performed the respiratory function test in accordance with the evaluation criteria.

The chest radiography of 127 (68.3%) patients was considered pathological, with an incidence of 17.7% for reticular/nodular opacities, 17.5% for hyperaeration, 17% for increased cardiothoracic index and 14.7% for fibrotic changes, respectively.

Among all patients, 67.1% was diagnosed with Chronic Obstructive Pulmonary Disease (COPD), 13.2% with ashtma, 6.2% with sequelae tuberculosis, 5% with chest wall deformity, 2.5% with interstitial lung disease/pneumoconious, 2.5% with lung cancer, 2.5% with sleep apnea syndrome, and 1% with bronchiectasis (Table 2). The highest mean age was in the COPD group with 69.5 years while the lowest mean age was in the chest wall deformity group with 32.8 years.

Furthermore, it was found out that 89.1% of patients also presented to other departments for assessment of disability other than the Chest Diseases Department, including 59.8% to the Physical Medicine and Rehabilitation, 58.3% to the Cardiology, 45.8% to the Eye Diseases, 27.9% to the Internal Diseases, 25.4% to the Otorhinolaryngology, 13.4% to the Neurology and 3.4% to the Oncology Departments (Table 3).

The disability rating due to respiratory system was 80% in 24.9% of patients, 40% in 34.7% of patients, and 20% in 40.4% of patients.

The results of our study showed that FEV_1 value was 40.2% in those with a 80% disability rating, 52.2% for those with a 40% disability rating, and 72.3% for those with a 20% disability rating.

The oxygen saturation was evaluated by pulse oximeter. The SpO_2 percentage was 86.9% in patients with a 80% disability rating, 94.2% in patients with a 40% disability rating, and 95.8% in patients with a 20% disability rating. There was a positive correlation between disability rating and age, and a negative correlation between FEV_1 and SpO_2 values (p: 0.002; p< 0.001; p< 0.001, respectively) (Table 4). Furthermore, the disability rating was higher in smokers than in non-smokers (p= 0.02).

DISCUSSION

A review of literature on disability in Turkey showed that disabled people were mainly studied for their general

Table 2. Frequency of respiratory disorders in disability

Diagnosis	Number	Percent
Chronic obstructive pulmonary disease	269	67.1
Asthma	53	13.2
Sequelae tuberculosis	25	6.2
Chest wall deformity	20	5
Interstitial lung disease/pneumoconious	10	2.5
Lung cancer	10	2.5
Sleep apnea syndrome	10	2.5
Bronchiectasis	4	1

Table 3. Applications to the other departments

Departments	Number	Percent
Physical medicine and rehabilitation	240	59.8
Cardiology	239	59.6
Eye diseases	184	45.9
Internal diseases	119	29.7
Otorhinolaryngology	111	27.7
Neurology	59	14.7
Oncology departments	16	4.0

Table 4. Respiratory disability rate

Disability rate (%)	Number (n)	Percent (%)	FEV_1 (%)	SpO_2 (%)
20%	162	40.4	72.3	95.8
40%	139	34.7	52.2	94.2
80%	100	24.9	40.2	86.9

It was performed by ANOVA test. Sig 0.00.

characteristics, but there was only a small number of studies on the basis of disease and branches. Our study showed that 4285 patients presented to the Medical Board of our hospital between January 2014 and July 2014 for assessment of their disability, with 9.3% having a respiratory disability. A study conducted in Sivas for evaluating the respiratory disability rating showed that 1.3% of presenting patients had respiratory disability [9]. The disability rating evaluated by the Chest Diseases Department in our study was higher than the one in the study by Berk et al. [9] Among our patients, 49.6% were from the city center, 37.4% from the districts of Van, and others from neighboring cities, from Ağrı, Siirt, Hakkari, Bitlis, and Muş, respectively. Van is one of the largest cities of Turkey. It has a population of 1.0855.42 people according to the Turkish Statistical Institute results of 2014. The study hospital is the referral center for the whole region for health problems. Our hospital provides health services not only for the city center of Van, but also for both districts of Van and neighboring cities.

The mean age of patients with a disability report from the Chest Diseases Department was 64.2 years. Of these patients, 59.4% were female, and 40.6% were male. The Turkey Disability Survey reported that among the disable population the number of men was 1.37 times higher than women [2,7]. Beşer et al. found that 59.7% of disabled people were men. In the study by Berk et al. reported that 87% of 135 patients were men [5,9]. Unlike those studies, there was a higher rate of female patients in our study.

The occupation of 9.9% patients was recorded as follows: housewife , farmer , industrial worker , construction worker , public servant and hairdresser, respectively. In the study by Berk et al. which examined 136 patients, the occupation of 121 patients (89%) was recorded [9].

Occupational disease was the main cause of disability, and occupational lung diseases rank first place among all occupational diseases in terms of incidence [10]. An analysis of our data showed our failure to record occupational history of all patients in the Medical Board reports. A review of the occupational diseases in Turkey showed that more than 70% of patients worked in sectors such as coal mining, metal and casting industry [11]. Particularly those workers serving for sectors with an exposure to fibrogenic powders such as silica, asbestos, and coal dust have severe impact on their respiratory functions [12].

In some developing countries, especially in rural areas, biomass is very fine particulate pollution arising from domestic fuel and food smoke exposure mostly affects women. [13,14]. A study conducted in Van by Özbay et al. showed that women who don't smoke but exposed to biomass smoke for 37.4 ± 10 years have sign of serious obstruction on Pulmonary Function Tests [15].

Infact, we can suggest that biomass exposure is an occupational risk factor for housewifes in our region, that may explain why females have more respiratory dissability in our study.

The major causes of respiratory disability include environmental and occupational exposures and smoking-related chronic respiratory diseases [16]. Smoking can increase respiratory symptoms, loss of lung function, and the progression of COPD [17].

Among all, 27.4% of patients were smokers, and 29.7% had biomass exposure. None of the reports indicated exposure to asbestos. The disability rating was higher in smokers than in non-smokers ($p= 0.02$).

A reduction can be expected in the disability rating of respiratory diseases with raising awareness and a strict monitoring of potential health problems in the related sectors, particularly providing information to local women about the lung diseases associated with inhalation of biomass smoke. During recent years using the slogan "smokeless zone" a high success for avoiding smoking has been achieved, pozitive impact on respiratory disability ratings will emerge in near future.

Spirometry is the most commonly performed test of measuring respiratory capacity. FVC is considered as the essential parameter in restrictive lung diseases, FEV_1 in obstructive lung diseases, and measurement of diffusion capacity in determining respiratory involvement [18]. FVC and FEV_1 measurements require good-cooperation of the patients. We found that 325 (81.2%) patients performed the respiratory function test in accordance with the evaluation criteria.

94.6% of patients performed the test in accordance with the evaluation criteria in Berks study [9]. The difference may be attributed to lack of Turkish literacy particularly of the elderly population in the region and following the directions for respiratory function as translated by a relative. In our study there was a negative correlation between FEV_1 value and disability ($p< 0.001$).

Since the relationship between Thoracic Computed Tomography and functional measurements was unclear, it is not routinely recommended for use in the assessment of disability [19]. Posteroanterior chest radiography is a commonly used method [20]. Radiologically the chest radiography of 68.3% patients was considered pathological, with reticular/nodular opacities, hyperaeration, increased

cardiothoracic index, and fibrotic changes being the most frequently reported pathologies.

The disability rating due to respiratory system was 80% in 24.9% of patients, 40% in 34.7% of patients, and 20% in 40.4% of patients.

Among all patients, 67.1% was diagnosed with Chronic Obstructive Pulmonary Disease (COPD), 13.2% with ashtma, 6.2% with sequelae tuberculosis, 5% with chest wall deformity, 2.5% with interstitial lung disease/pneumoconious, 2.5% with lung cancer, 2.5% with sleep apnea syndrome, and 1% with bronchiectasis.

The ILO (International Labour Organization) noticed that, the work-related illnesses and accidents cost direct and indirect damage to the economy of countries in the World, and the global cost is supposed to be at least 2.8 trillion dollars [21].

In recent years, Disability Adjusted Life Years (DALY) used by WHO (World Health Organisation) for assesment morbidity and burden of desease.

DALY is defined as early death and the sum of years lost due to disability [22]. COPD is an important morbidity reason for DALY [23,24].

The severity of asthma determines the cost of the disease. Direct costs of patients with moderate or severe persistent asthma were 2.5-2.8 times more than those with mild intermittent asthma [25,26].

The highest mean age was in the COPD group with 69.5 years while the lowest mean age was in the chest wall deformity group with 32.8 years. There was a positive correlation between disability rating and age.

Furthermore, it was found out that 89.1% of patients also presented to other departments for assessment of disability other than the Chest Diseases Department, including Physical Medicine and Rehabilitation, Cardiology, Eye Diseases, Internal Diseases, Otorhinolaryngology, Neurology and Oncology Departments. Since the patients were in a similar age group, hypertension and cardiac diseases can be considered as concomittant diseases due to presence of similar risk factors such as gonarthros, cataract and smoking.

The SpO_2 percentage was 86.9% in patients with 80% disability rating, 94.2% in patients with 40% disability rating, and 95.8% in patients with 20% disability rating. As a result, there was a positive relationship between a lower saturation and higher disability rating ($p< 001$).

In the study by Berk et al., arterial blood gas was tested in more than half of the patients, and a positive correlation was found between pCO_2 and respiratory involvement [9]. However, recent studies have reported that arterial blood gas test did not have any additional contribution to the respiratory function tests in assessing disability [27].

Electromagnetic energy from motion artifact, low perfusion, skin pigmentation and dark nail polish, tachycardia, cellular phones and electrocautery devices results in limitation in use of pulse oxymeter [28-30].

Many oximeter producer defines the 95% confidence interval as 4 ± for SpO_2 when SaO_2 (Oxigen saturation) is over 80%. The accuracy of pulse oximeter is reduced when SaO_2 is below 80% [18,19].

However, since patient evaluation for medical board reports is made at the setting of outpatient clinics in daily practice, measurement of saturation by pulse oximeter rather than arterial blood gas testing might be much more practical like we did.

CONCLUSION

In conclusion, the number of patients presenting for assessment of their disability in order to enjoy several rights is consistently increasing. The present study is one of the rare studies examining the respiratory disability in Turkey. Definition of diseases associated with respiratory disability is important in identifying priorities for preventive health services. Our results may provide statistical information on patients with respiratory disability in our region and determine the requirements of these patients and enhance data with a focus on resources for these requirements. Any comparative studies by provinces may provide information on the prevalence and rate of health problems, generating data for social and legal arrangements in the future, and thus contribute to a better management of the disability assessment process.

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REVIEW

History of Lung Transplantation

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Abstract

History of lung transplantation in the world can be traced back to the early years of the 20th century when experimental vascular anastomotic techniques were developed by Carrel and Guthrie, followed by transplantation of thoracic organs on animal models by Demikhov and finally it was James Hardy who did the first lung transplantation attempt on human. But it was not until the discovery of cyclosporine and development of better surgical techniques that success could be achieved in that field by the Toronto Lung Transplant Group led by Joel Cooper. Up to the present day, over 51.000 lung transplants were performed in the world at different centers. The start of lung transplantation in Turkey has been delayed for various reasons. From 1998 on, there were several attempts but the first successful lung transplant was performed at Sureyyapasa Hospital in 2009. Today there are four lung transplant centers in Turkey; two in Istanbul, one in Ankara and another one in Izmir. Three lung transplant centers from Istanbul which belong to private sector have newly applied for licence from the Ministry of Health.

KEYWORDS: History, lung transplantation, Turkey

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History of lung transplantation is written by endeavors and courage of people who were desperately in search of hope.

Dr. James Hardy from Jackson Mississippi, USA was the first surgeon in the world to perform lung transplantation in man in 1963. The patient was a 58-year old man who had lung cancer involving the left main airway and obstructing distal airways resulting in lung collapse and recurrent pneumonia. While the patient was serving a life sentence in prison, Hardy outlined the potential complications and risks with him in detail and he agreed to proceed [1-3]. This was the time the countdown for a donor and prospect transplant started. Both medically and legally, such a patient would not be an appropriate candidate for lung transplantation at any transplant center at this time and day. No matter what opponents claim, this was a challenging and risky task both for Hardy and his patient with their own self-explanatory reasons and motivation.

The donor was taken to the operating room for retrieval while the recipient was prepared for transplantation in the adjacent operating room almost simultaneously. Both operations were remarkably uncomplicated and the recipient began breathing spontaneously. Indeed, the arterial oxygen saturation improved from 87% before to 98% immediately after the transplant. Chest X-rays and an angiogram confirmed that the transplanted lung was very well ventilated and perfused [2]. Surgeons had done their jobs perfectly well. The cornerstones of a successful lung transplantation today are good donor, good recipient and good surgery followed by meticulous early postoperative management. The donor and recipient selection in the very first lung transplantation of the world was maybe arbitrary due to aforementioned reasons and not so ideal, but the surgery had gone smooth owing to surgeons' interest and experience. The immunosuppressive regimen consisted of azathioprine, prednisone, and cobalt radiation to the mediastinum and thymus. Notably, cyclosporine and tacrolimus, which are the mainstays of immunosuppression in modern transplantation, had not yet been discovered [2,3]. Those were the times 'less was more' and against all odds, this was the first, but not the only or the final success in lung transplant history.

Every single step, every attempt that we find worthy of mentioning today, be it from Hardy, Carrel, Guthrie, Demikhov are bricks in the gigantic wall of lung transplantation. If it were not for Alexis Carrel and Charles Guthrie, techniques of anastomosis of intrathoracic vessels and suturing models would not have developed as much. It was them very early in the first years of last century who did animal experiments trying to connect vessels. Their attempts have highlighted cardiovascular surgery and Carrell had won the 1912 Nobel Prize in Physiology and Medicine [2]. In 1946 the Russian

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physiologist Demikhov had transplanted the heart and lungs of dogs as a single graft and reported the first successful canine lung transplantation in 1946 and Metras from Marseilles in 1950 [4,5]. The techniques of anastomosis of these experimental surgeons had highlighted Hardy's transplant surgery.

Let's go back to Hardy's recipient. After the initial success, the patient developed progressive kidney failure and became increasingly malnourished. He was started on peritoneal dialysis but died only eighteen days after the transplant due to uncontrollable renal failure. An autopsy showed no evidence of rejection in the transplanted lung. Despite the ultimate outcome, this case encouraged the field of lung transplantation by demonstrating that the transplanted lung could function physiologically and rejection could be averted with the available immunosuppressants, at least for a short time. However, over the following ten years, that is to say until early seventies, only 36 lung transplants were performed worldwide and the majority of recipients unfortunately died within a few days while only two recipients survived more than a month. The leading cause of death, and the primary obstacle to better outcomes was poor healing of the airway anastomosis, which sometimes eroded into adjacent vessels and led to massive bleeding into the lung [2].

The 1980's were for sure the most productive decade for lung transplantation. In 1981, Drs. Norman Shumway and Bruce Reitz at Stanford University performed three heart-lung transplants two of which were successful. These recipients were still alive when the team reported their results in 1982 [6]. One recipient died four days after the operation because of multi-organ failure. Dr. Shumway attributed the success to refining surgical techniques through primate experimentation and the advent of cyclosporine, which reduced the necessary steroid doses thus mitigating their negative impact on anastomotic site healing. In the meantime, Drs Pearson and Cooper from Toronto General Hospital, Canada were studying the problem of posttransplant donor bronchial ischemia in their laboratories [2].

In 1983, the Toronto Lung Transplant Group performed in fact the very first successful lung transplant in the world [7]. This was a project by Joel Cooper to bring lung transplantation to clinical practice. After being approved by the ethical committee of the Toronto General Hospital, candidates preferably under 50 years of age, with totally disabling primary pathology of the lung, unable to perform any tasks , judged to have less than 6 months of life expectancy were recruited as experimental transplant patients. To date, cystic fibrosis is the leading cause of lung transplant in the pediatric group and is the third in the adult group. Cystic fibrosis patients which are today undoubtedly on waiting lists of all transplant centers in the world were not considered at that time in that project due to possible septic and surgical complications. Ron Grossman, the pulmonologist of the team, travelled all over Canada and the USA to assess transplant candidates. The recipient was finally decided to be a 58-year old man with pulmonary fibrosis. Although he was informed by doctors about the complications of transplant and that 43 lung transplant attempts in the world had failed up to that time, he said in a very brave mood "It is my privilige to be the 44th patient". The patient had pulmonary fibrosis and a single lung transplant would be sufficient. The operation and early post-operative course was fairly uncomplicated. He was treated with cyclosporine and azathioprine for immunosuppression and initially did not receive steroids to minimize the risk of airway anastomotic dehiscence, because in those days it was the most feared deadly complication. However, in the first two weeks he developed two episodes of rejection that resulted in respiratory failure and thus, required steroids and lymphocyte depletion. The recipient ultimately recovered and was discharged home. When the group reported their experience in 1986, he was alive and leading a normal lifestyle [7]. He survived for another 4 years afterwards. This success was remarkably encouraging for pulmonary physicians and patients with lung disease, but the early rejection was an ominous prediction of future obstacles and limitations. First bilateral lung transplantation was also performed at Toronto General Hospital in 1986. Later in 1988 cystic fibrosis patients were recruited and transplanted again at the same center. In the meantime, in Europe, active lung transplant programs were being developed at Papworth, Newcastle, Harefield in the United Kingdom, in Paris, Hannover and Vienna in central Europe [2,7,8].

Over the ensuing decade, the number of lung transplants performed worldwide increased rapidly. In 1987, approximately 45 transplants were performed, and by 1990, over 400 were performed worldwide. Activity continued to increase rapidly until the mid 1990's when the number of annual transplants plateaued at approximately 1400. In recent years, the number of transplants has increased to approximately 2200 per year. Over the years, outcomes have improved as surgical techniques, donor and recipient selection, and medical therapy have been refined. In fact, the median survival of patients transplanted between 2000 and 2006 was 5.5 years compared to 4 years for those transplanted between 1988 and 1994. However, outcomes in the modern era remain far from ideal as chronic rejection has emerged as the leading obstacle to better long-term survival [2]. Likewise, the shortage of suitable donor organs remains the primary limitation to the more widespread use of lung transplantation which is also the case in Turkey.

The Situation in Turkey

Turkey has a population of 75 million and the number of organ donations in Turkey is 4.6 pmp (per million population). Solid organ transplants have started years ago in our country and are being done with considerable success. Contrary to international data, most of solid organ transplants are being done from living donors [9].

The start of lung transplantation in Turkey was belated for several reasons. One of the most important was thoracic surgeons' not being allowed to perform lung transplantations due to health regulations. In fact it was cardiothoracic surgeons who were allowed, but thoracic surgery and cardiovascular surgery were recognized as separate specialties in mid- eighties and it was a cardiothoracic surgeon who attempted the very first heart-lung transplant surgery in Turkey which will be mentioned in the folowing section. Donor shortage was another obstacle. Since lung

transplantation requires serious team-work at multidisciplinary hospitals, transplantation was seen as a task that should be shouldered by universities. Interest and demand was low and surgeons were not motivated. Pulmonologists were not ready to evaluate and manage transplant patients. Attempts were made starting from 1998, but the real success, the patient's possibility of being discharged from the hospital and surviving for years, was not apparent until 2009.

Attempts of Heart-Lung and Lung Transplantation in Turkey

The first pediatric heart-lung transplant patient was operated by Oztekin Oto at Dokuz Eylul University Hospital in 1998. Six heart-lung transplants had been carried out in Turkey up to that time, but none of the patients had survived for long periods. Rather than scientific literature, information depends on personal communication with cardiovascular transplant centers within the country. Only the first patient is reported to have lived for nine months [10-13].

Göksel Kalaycı from Istanbul University attempted an adult bilateral lung transplantation on 11 October 2004. The patient was a 44 year-old male idiopathic pulmonary fibrosis (IPF) case with end-stage pulmonary insufficiency. He had very high pulmonary arterial pressures and his kidney function was suboptimal. The donor was a very young female patient with a clear chest X-ray and quite favorable blood gases. The bilateral sequential single lung transplantation was carried out under cardiopulmonary by-pass. The patient had a bleeding disorder thereafter and died from disseminated intravascular coagulopathy and multiorgan failure on the 11th postoperative day. The postmortem biopsies from the lung showed acute alveolar damage. This very first case was followed by another IPF case the same year and another case in 2007, but none of the patients survived the early postoperative period. Data concerning those patients has been obtained by personal communication with Alper Toker who was in the transplant team in those days. In 2008 an Eisenmenger patient received a heart-lung transplant at Ege University and this patient is said to have lived only for a few months .

In 2012 another patient with heart failure and high pulmonary vascular resistance received a heart-lung transplant at Istanbul Kartal Kosuyolu Yuksek Ihtisas Teaching Hospital for Cardiovascular Diseases and Surgery, mainly recognized as a cardiac transplant hospital and a reference center in Turkey since 1989. The patient did not survive the early posttransplant phase due to disseminated intravascular coagulopathy and ensuing multiorgan failure.

The First Successful Lung Transplantation in Turkey

The first long-time lung transplant survivor of Turkey was a 34 year-old silicosis patient who underwent single lung transplantation at Sureyyapasa Teaching Hospital for Pulmonary Diseases and Thoracic Surgery on 7 March 2009. The procedure was carried out by a surgical team headed by Cemal Asım Kutlu at a state teaching hospital. There was support from the Ministry of Health, hospital director Semih Halezeroğlu, chief of Pulmonology Attila Saygı and a group of specialists from the hospital in related fields. This operation has given hope and opportunity both to patients and doctors in the country [10].

Although criticized and questioned for quite a long time, this very first case started a surge of interest in lung transplantation in the country. Soon after, Mustafa Özbaran performed the first bilateral pediatric lung transplantation at Ege University on 8 April 2009 [14]. The patient, a 15-year-old teenager, primarily diagnosed with bronchiolitis obliterans who was in the latest stage of his disease, dependent on noninvasive ventilation and continuous oxygen, lived for nearly 3 years after the operation. He was well until he developed chronic rejection late in the second year and died due to bleeding complications after retransplantation was attempted at Kartal Kosuyolu Yuksek Ihtisas Teaching Hospital for Cardiovascular Diseases and Surgery [10].

Several attempts were made in Turkey starting from 1998, but the real success, with the possibility of the patient being discharged from hospital and surviving for years, was not apparent until 2009. The first author of this review, as the pulmonologist of the team, witnessed the first successful lung transplant operation. What happened at Sureyyapasa in those days was mainly the result of the synergy of a group of enthusiastic doctors committed to establishing a lung transplant program at their hospital. Up to that time, although Turkey had a few transplant centers, prominent institutions, mainly university hospitals, were reluctant to enter this arena because of concerns about outcomes and difficulties concerning boundaries of specialties to deal with lung transplantation. With this historical backround in 2007, transplant surgeons were determined to change the regulations concerning lung transplantation in Turkey. It took quite a long time for negotiations at the level of the Ministry of Health to make the desired change in the regulation, the team at Sureyyapasa namely Sureyyapasa Lung Transplantation Study Group made the start for a visionary change. Medical and technical needs were met, members of the team were sent abroad to have proper training in transplantation Weekly seminars and literature reviews were organized with invited speakers from transplant centers. Logistic problems and legislative issues were addressed. Finally the certification of Sureyyapasa as a transplant hospital was completed in December 2008. In the meantime, patients were accepted and evaluated preoperatively to form a waiting list. In a few months' time we had nearly 30 cases on the waiting list because the demand from the doctors and patients increased as soon as news spread in the medical community [10].

There was both excitement and anxiety when the first lung donation was announced to Sureyyapasa late in the afternoon on a spring day (6 March 2009). The donor was a 13-year-old female patient who had brain damage due to an accident and was intubated for 72 hours. Her chest X-ray and bronchoscopy findings were normal. PaO_2/FiO_2 was greater than 500 which was quite good [10].

The only difficulty would be to find a recipient with a small-sized chest cavity. When we looked at our waiting list, we found that the matching recipient was a 34 year-old dental technician who suffered from silicosis related to his occupation. He was on oxygen and his condition was deteriorating rapidly. The first long-time survivor of lung transplantation in Belgium was a silicotic patient as well (14 November 1968). The surgeon was Fritz Derom and the

patient had survived for 10 months.This patient gave us hope for our very first patient [5].

The implantation of the new lung was complete at dawn and the patient was transfered to the intensive care unit with his new left lung. In spite of complications, the patient was extubated at 15 hours. There was great joy and excitement at the hospital and the news spread quite fast in medical surroundings. The very first patient of lung transplantation lived for 3.5 years. He endured rejection episodes and infections but developed bronchiolitis obliterans syndrome earlier than expected mainly owing to his medical noncompliance and gastroesophageal reflux [10].

Sureyyapasa Lung Transplant Group had one more survivor, but the other patients were either lost due to surgical problems or primary graft dysfunction and ensuing infections. We announced our data at national meetings which was met by critism. We were questioned as to whether we were right in our patient and donor selection, harvesting, organ procurement and matching. We had limited resources. Administrative problems with drug maintenance, drug level monitoring, and bronchoscopy practice complicated the course of establishing a well-organized program. We were accused of draining our hospital's resources into a costly procedure, but having less favorable prognosis when compared to outcomes of world centers. On the other hand, there was a huge demand both from our patients and their families which was a source of motivation but a great responsibility and burden at the same time. We were under the scrutiny of the medical community, which put much pressure on team members. The operations and the postoperative period were also questionable. These were all part of a lung transplant program and our circumstances were not perfect, starting with the choice of recipients. Some of our cases were functionally too desperate to survive a critical operation like transplantation with a low capacity of rehabilitation [10]. Besides, pulmonary rehabilitation program which is a very important part of a lung transplant program had not started at Sureyyapasa Hospital at that time.

Our patients, some of them being disabled by their respiratory insufficiency, prolonged corticosteroid usage were on noninvasive ventilators, bedridden and psychologically and socially in poor condition. These were relative or sometimes arguably absolute contraindications to transplantation, but we also had patients that surprised us with their prognosis having a strong drive to survive in spite of all complications. In the meanime Sureyyapasa Lung Transplant Group had to withstand administrative obstacles like medical expenses, drug maintanence, drug level monitoring, bronchoscopy performances, all of which are actually essential parts of a transplant program. Several prominent centers, famous for solid organ transplantations, found it challenging to enter the transplant arena because of concerns about outcomes and drawbacks of current circumstances in the country. Two years later, determined to carry on, Sureyyapasa Lung Transplant Group moved to another hospital (Kartal Kosuyolu Yuksek Ihtisas) to search for better surgical and intensive care possibilities. Here severely ill patients with comorbidities, heart-lung transplant candidates, even patients with multiorgan failure, a higher number of borderline donors and overall reduced resources in healthcare due to changes in health management were challenges the team was faced with. In 2011, another transplant team at Yedikule Training and Research Hospital for Pulmonary Diseases and Thoracic Surgery was on their way for successful transplantations. Better equipped and prepared, this team has transplanted 30 patients up to the present day; one of them being a retransplant. Another transplant center in Ankara (Yuksek Ihtisas Training and Research Hospital) entered the arena two years later and has transplanted 11 patients so far. The directors of those seperate transplant centers should be consulted about the mortality and morbidity rates of their transplants, because as far as the authors of this review are informed, there are no published data concerning early and late postoperative complications. Also the lung transplant statistics of Turkish Ministry of Health give contradictory results and cannot be accessed by all physicians.

Currently, there are 4 transplant centers in Turkey, 2 in Istanbul, one in Ankara and İzmir each. These are namely Istanbul University Medical Faculty Hospital, Marmara University Hospital, Ankara Yuksek Ihtisas Training and Research Hospital, Izmir Ege University Hospital. Three other centers in private sector in Istanbul have applied for a transplant licence from the Ministry of Health. As far as complications, medical management, and risk of mortality are concerned, lung transplantation prevails over other solid organ transplants and necessitates a serious team working, personal dedication and sacrifice. We believe the future of lung transplantation in Turkey will be brighter and more fruitful if the transplant community works in collaboration. Surgeons have exemplified their enthusiasm and dominance whereas pulmonologists have stood at a distance to lung transplantation. Surgeons should not be tempted by the societal demand and the sentimental will to save every single patient. Liberilisation of donor criteria have already increased the number of donor lungs that are transplanted, but we should be cautious about determining the quality of donor lung, because this affects both the early and late postoperative course. Transplanting more and more patients on extracorporal membrane oxygenation (ECMO) means sicker patients are accepted in the program which might automatically lower the rate of success. It is also a universal debate that is going on if it would be appropriate to use a good donor for a very sick patient in a medium of organ shortage.

What we need to see in the 21st century of Turkey is that lung transplantation is not only a surgical field of interest, but an arena where pulmonologists work for the welfare of the patient thoroughout the entire pre- and posttransplant phases. What was at the beginning new and exceptional should now turn out to be expected and routine. Patients who suffer from end-stage respiratory failure should not be referred to transplant centers only when circumstances dictate, but rather earlier on the course of their diseases. "Nothing to lose" approach is not something that can be applied to desperately ill patients. Some transplant candidates are too sick to tolerate a transplant operation. So timely referral of patients to transplant centers is of utmost importance.

To conclude, we should work hand- in- hand to overcome administrative, medical and surgical issues related to lung transplantation in Turkey and provide a better service to our patients. Transplant history will not be written by excuses and delays, but by responsible attitude and active contribution.

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CASE REPORT

Pneumomediastinum After Difficult Vaginal Delivery

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Abstract

17-year-old primigravida patient presented with chest pain, dyspnea, sore throat and a sensation of swelling in the neck and throat approximately 3 hours after difficult vaginal delivery at home. Breath sounds were equal bilaterally. Physical examination revealed subcutaneous emphysema that expanded from the anterior thorax to the neck. Posteroanterior (PA) chest X-ray showed air in the neck and thoracic computed tomography showed pneumomediastinum. The patient was admitted to our clinic and was started on ampicillin-sulbactam 3 x 1 grams iv, paracetamol 2 x 1000 mg and 3 L/min of oxygen therapy. C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR), which were monitored on a daily basis, showed decline. Repeated chest X-rays did not show any progression. The patient was clinically stable and was discharged from the hospital on the third day. Currently in her third month of follow-up, the patient is stable.

KEYWORDS: Delivery, pneumomediastinum, pneumothorax

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INTRODUCTION

Spontaneous pneumomediastinum is defined as free air in the mediastinum without trauma or a medical problem, and is rarely encountered [1,2]. Spontaneous pneumomediastinum is a clinical entity first described by Hamman in 1939 [3]. Conditions that increase intrathoracic pressure, such as esophageal rupture, acute asthma attack and trauma can be named as its reasons [4]. This study presents the case of spontaneous pneumomediastinum and pneumothorax that developed in a patient who had difficult vaginal delivery at home by reviewing the literature.

CASE PRESENTATION

17-year-old primigravida patient applied to our center with chest pain, dyspnea, sore throat and a sensation of swelling in the neck and throat approximately 3 hours after difficult vaginal delivery at home. Breath sounds were equal bilaterally. Physical examination revealed subcutaneous emphysema that expanded from the anterior thorax to the neck. Other physical examinations were evaluated normal. Leucocytosis was present in complete blood count during admission. It was seen that the patient's erythrocyte sedimentation rate (ESR) and CRP values were raised. Images consistent with subcutaneous emphysema in the neck (Figure 1) were seen in the postero-anterior chest X-ray (PA CX), and an image belonging to pneumomediastinum and bilateral minimum pneumothorax was assessed present on Thoracic Computed Tomography (CT) (Figures 2A,B). The patient, who was admitted to our clinic, was started on ampicillin sulbactam 3 x 1 grams iv, paracetamol 2 x 1000 mg and 3 L/min of oxygen therapy. It was seen in daily CRP and ESR follow-ups that there was a decline. Progression was not seen in PA AC graphy follow-ups. The clinically stable patient was discharged on day 3. The patient, who is currently on her third month follow-up, is stable.

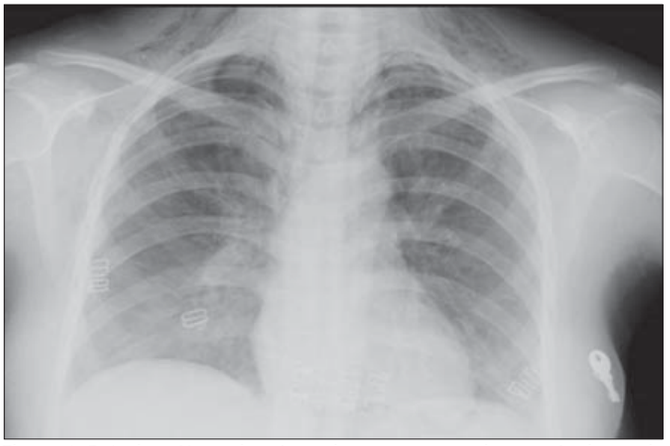

Figure 1. P-A chest X-ray showing subcutaneous emphysema in the neck.

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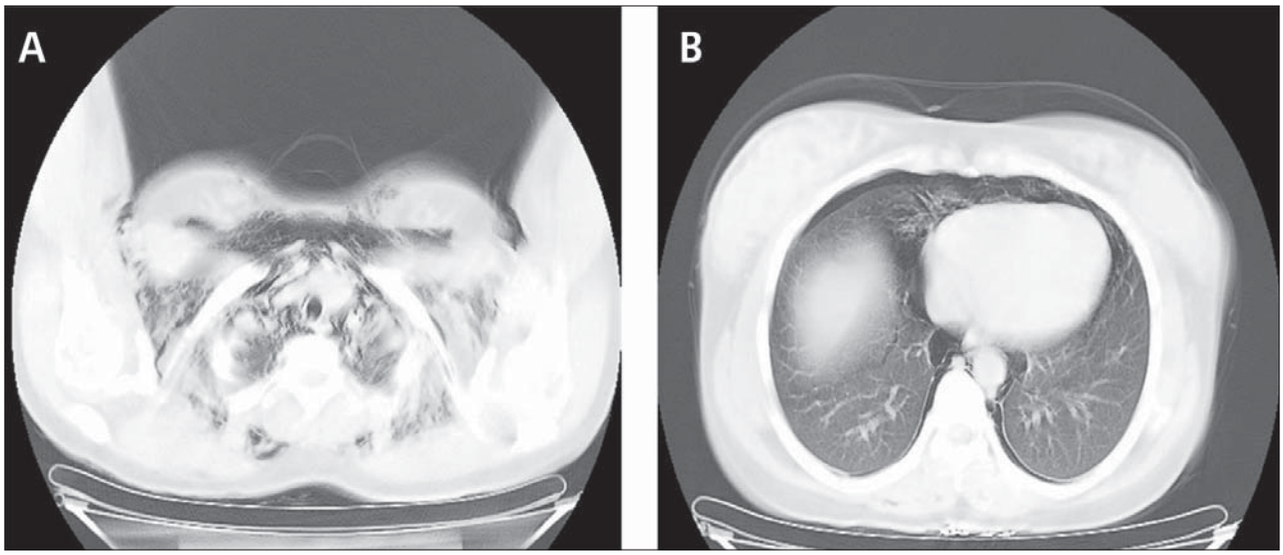

Figure 2. Thoracic CT image.

DISCUSSION

Apart from trauma, spontaneous pneumomediastinum and spontaneous pneumothorax that develop during pregnancy and maternity are rare occurrences [5,6]. Generally chest pain which is present in the clinical symptoms of the patients is accompanied with dyspnoea, dysphonia and subcutaneous emphysema in the neck [7]. Complaints start during delivery or immediately postpartum; however, this condition can be described as far as the postpartum second month [4]. Since the risk of venous thromboembolism increases in pregnant women, the risk of pulmonary thromboembolism also increases in the postpartum period, and pulmonary thromboembolism should be kept in mind in patients presenting with dyspnoea in the postpartum period [7,8]. The patient's complaints began approximately three hours postpartum, and the patient presented to our clinic with chest pain, dyspnea and subcutaneous emphysema in the neck region, which are findings also seen in the literature.

Many lung diseases including bronchiectasis, asthma, emphysema, and interstitial lung diseases are predisposing factors in the development of spontaneous pneumomediastinum [1]. These diseases that can cause spontaneous pneumomediastinum were not present in our patient.

Subcutaneous emphysema spreading to the neck is observed in Boerhaave syndrome originating from the oesophagus tissue. While Boerhaave syndrome is associated with vomiting during pregnancy, it has not been described during delivery. The source of free air in spontaneous pneumomediastinum is the lungs. Ruptures in small bronchial or alveolar level and barotrauma caused by positive pressure ventilation in the perinatal period can develop as a result of Valsalva-type manoeuvre that increase intraluminal pressure [7]. Prolonging of the second phase of delivery or the presence of cephalopelvic disproportion increases the risk of spontaneous pneumomediastinum development since intrathoracic pressure is going to increase due to the fact that the Valsalva manoeuvre will be specifically more in this period [4]. It was stated that our patient had a difficult delivery outside hospital conditions.

The diagnosis of spontaneous pneumomediastinum is made through chest roentgenogram or thoracic CT. Moreover, esophagogastroscopy and bronchoscopy are among the recommended diagnostic tests [1]. Chest roentgenogram and thoracic CT were performed on our patient but esophagogastroscopy and bronchoscopy could not be performed.

Follow-up period of these patients should be at least 24 to 36 hours [9]. Bed rest, oxygen inhalation, analgesic treatment, and antibiotherapy against the risk of mediastinitis are recommended in treatment [4,10,11]. Our case was followed up 48 hours in hospital conditions, and oxygen inhalation, analgesic treatment and prophylactic antibiotherapy were carried out throughout the follow-up.

Pneumothorax and spontaneous pneumomediastinum should rank among diagnosis in dyspnea complaint that could develop after difficult vaginal delivery.

Author Contributions: Concept - A.S., O.A.; Design - A.S., O.A.; Supervision - A.S., O.A.; Resources - A.S.; Materials - A.S.; Data Collection and/or Processing - O.A.; Analysis and/or Interpretation - A.S., O.A.; Literature Search - A.S., O.A.; Writing Manuscript - A.S., O.A.; Critical Review - A.S., O.A.

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CASE REPORT

Unusual Radiological Sign in Bronchial Atresia

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Abstract

Bronchial atresia is usually diagnosed by incidentally detecting opacitiy at hilar ragion and hyperinflation around this opacity on chest X-ray. It may rarely be detected as air sac like atresic bronchus. The breath sounds in the right hemithorax were heard less when compared to the left hemithorax in the auscultation of a 16-year-old male patient with allergic rhinitis. The patient had no pulmonary complaints, and this finding was not recorded in his previous follow-up. In order to determine the etiology of hyperinflation seen on chest X-ray, computed tomography was performed. Hyperinflation was identified in the lower lobe superior segment of the right lung, which could be secondary to bronchial atresia. It was confirmed that in the evaluation of computed tomography with three-dimensional reconstruction, lower lobe superior segment bronchus of the right lung was atresic and contrary to expected mucus opacity in the distal of atresia, dilated bronchus was filled with air. This case was especially presented to lay emphasis on careful auscultation and share its unusual radiological presentation which had been reported twice before.

KEYWORDS: Bronchial atresia, bronchial diseases, congenital, hyperinflation, radiology

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INTRODUCTION

Congenital lung malformations are mostly diagnosed prenatally or in early childhood. However, it can be detected in later periods and even coincidentally, with unrelated clinical symptoms [1]. Bronchial atresia, which is one of the congenital lung malformations that receive late diagnosis, develops as a result of a cut in the continuity of lobar, segmental or subsegmental bronchus. Bronchial atresia is characterized by an increase in inflation in the lung region inflated by the atresic bronchus and accumulation of mucus in the distal of the atresic bronchus [2]. Generally the diagnosis is made by lung graphy with a coincidental detection of opacity in the hilar region and increase in the inflation around it [3]. Rarely, it can be diagnosed by seeing air-fluid level in the distal of the atresic bronchus [4]. The air sac shape of the atresic bronchus is very rare and has been reported twice in the literature.

This study presented the case of a patient with allergic rhinitis, who was diagnosed with atypical bronchial atresia as a result of the radiological examinations performed upon hearing less breath sounds in lung auscultation.

CASE PRESENTATION

A 16-year-old male patient had been followed up in our polyclinic with a diagnosis of seasonal allergic rhinitis for four years when it was detected during his routine physical examination that the breath sounds in the right hemithorax were heard less when compared to the left hemithorax. There was no peculiarity in patient history and laboratory findings, and pulmonary function test was within normal limits. Upon detecting hyperinflation in the right lung on lung graphy (Figure 1), lung tomography was performed to have an etiologic evaluation. On lung tomography, hyperinflation was identified in the lower lobe superior segment of the right lung, which was thought to be secondary to bronchial atresia or bronchus obstruction. Flexible fiber optic bronchoscopy was conducted in an attempt to investigate the reasons of bronchus obstruction, particularly foreign body aspiration. Trachea and major bronchi were normal on bronchoscopy; however double entry variation anomaly was detected coincidentally. It was detected in the evaluation of the lung tomography with a three-dimensional reconstruction that there was not truncus exit point in the lower lobe superior segment of the right lung and that there was a hyperlucent volume in low vascularity that displaced other lung segments due to hyperinflation in the localization of right lung lower lobe superior segment. A bronchial tree wider than usual and showing branching to the periphery was present within the identified hyperlucent volume. This bronchial tree could draw close to bronchial structures in the hilus at most 6.8 mm. The air-filled bronchiectasis structure, unrelated

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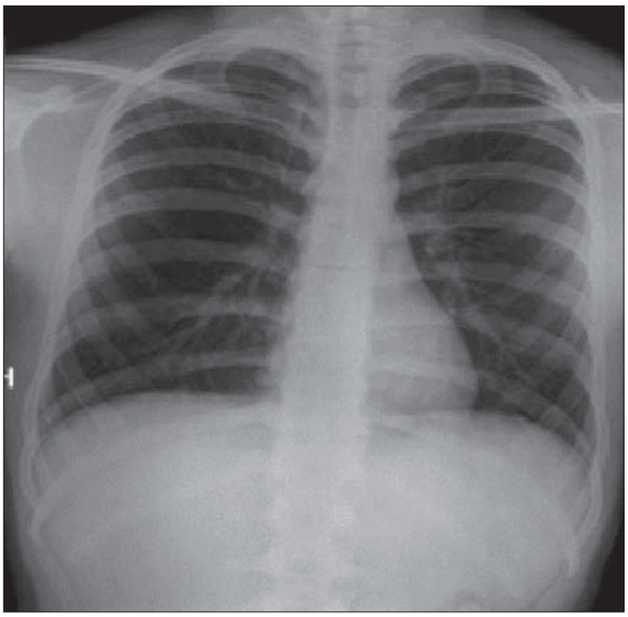

Figure 1. Hyperinflation in the right lung on the posteroanterior lung graphy.

to the bronchial structures in the hilus, ended with a sharp point proximally (Figure 2).

Since congenital cardiovascular anomalies can sometimes accompany bronchial atresia, cardiologic evaluation was performed, revealing no pathologies. Although the case was asymptomatic, since there was hyperinflation in a very wide region of the lung, the case was closely followed up in terms of probable infection and progression.

DISCUSSION

The first case of bronchial atresia was reported by Ramsay and Byron in 1953 [5]. The main reason of bronchial atresia is unknown. The localization of atresia is linked to the time intrauterine is affected. If fetal development is affected on the 5th, 6th and 16th weeks, lobar, segmental and subsegmental bronchial atresia are seen respectively [6]. Cases have been reported, where bronchial atresia is mixed or coexists with other congenital lobar emphysema or congenital cystic malformation. In a recent study, it has been put forward that bronchial atresia is a component of a series of congenital lung anomalies. The formation time of bronchial atresia in fetal period and its response level are associated with the etiology causing this anomaly [2].

Air access to the lung segment ventilated by the atresic bronchus happens with Kohnpores and Lambert channels. As these allow for more air flow during inspiration in proportion to expiration, hyperinflation develops in the lung segment ventilated by the atresic bronchus. Generally bronchial mucocele occurs as a result of mucus accumulation in the distal of the the atresic bronchus [7]. Bronchial atresia is usually asymptomatic, just as it was in our case; however, it may cause repetitive lung infection, cough, wheezing, and dyspnea in some cases [8,9]. It has been reported to cause spontaneous pneumothorax very rarely [10].

Generally, lung tomography is sufficient for the diagnosis of congenital bronchial atresia. Characteristics finding of bronchial atresia on lung tomography is the image of air and mucus-filled, widened bronchus [11-13]. The surrounding area of the mucus-filled, widened bronchus is seen hyperlucent with focal parenchymal oligemia and air trapping that occur as a result of hypoxic vasoconstriction and intrapulmonary vascular compression [13]. Bronchoscopy can be used in terms of the diagnosis of proximal atresia and differential diagnosis [8,9]. Mucocele, which is a typical finding of bronchial atresia on lung graphy, can be seen as nodule close to the hilar region, ovoid, bronchus structure or tubular [14]. Until now, the dilated bronchus has been shown in two other cases to be filled with air instead of mucus, just as it was in our case [4,15]. Congenital diseases or diseases causing acquired bronchus obstruction should be considered in differential diagnosis.

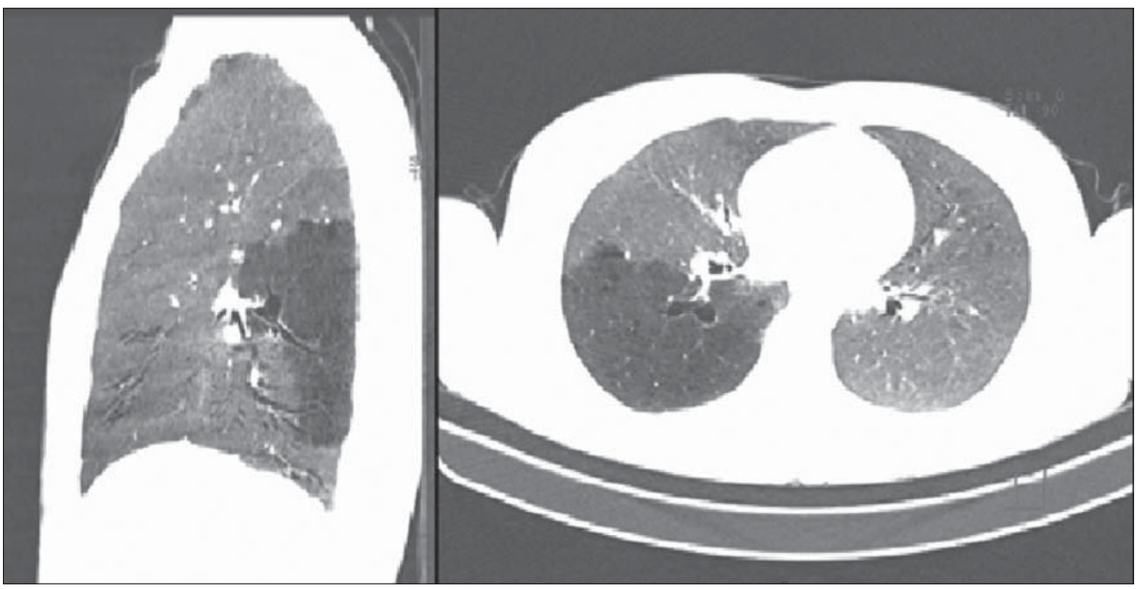

Figure 2. The atresic image of the lower lobe superior segment bronchus of the right lung on the reconstruction of thoracic computed tomography and it is seen that the dilated bronchus is filled with air contrary to the expected mucus opacity in the distal of the atresia.

The diagnosis of bronchial atresia is made late since it does not usually cause symptoms [16]. It is diagnosed at about 17 years of age. Two thirds of the reported cases are patients that have not had pulmonary complaints until that day and that have received coincidental diagnosis as a result of the performed lung graphy, just as it was in our case. Treatment is not recommended in asymptomatic patients. Surgical excision is needed if complications, primarily infection, secondary to atresic bronchus develop [17].

Even though classic radiological finding is defined as the mucus opacity in the distal of the atresia and rarely as the opacity that gives air-fluid level in bronchial atresia, the dilated bronchus can be seen as fully filled with air, just as it was in our case. This case was presented in order to emphasize the importance of careful auscultation during physical examination and share the atypical radiologic presentation that has only been reported twice in the literature.

Author Contributions: Concept - S.K., D.C.; Design - S.B.E., S.K.; Supervision - H.A., A.K.; Resources - S.K., S.B.E.; Materials - S.K.; Data Collection and/or Processing - S.B.E., R.D., S.K.; Analysis and/or Interpretation - H.A., D.C., A.K.; Literature Search -R.D.; Writing Manuscript - R.D., S.K.; Critical Review - D.C., H.A., A.K.

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CASE REPORT

Nebulized Lidocaine as an Alternative Therapy for Reactive Airway Dysfunction Syndrome

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Abstract

Reactive airway dysfunction syndrome (RADS) is a variant of irritant-induced asthma that develops in subjects without prior bronchoobstructive disease, following high-level exposure to nonimmunogenic irritants. Recommended maintenance treatment for RADS is not different from asthma. But in some cases, severe symptoms may persist despite the bronchodilators and corticosteroids. We describe the first case of a patient with RADS, unresponsive to all medical agents, who was successfully treated with lidocaine.

KEYWORDS: Asthma, sodium hypochloride, lidocaine

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INTRODUCTION

Reactive airway dysfunction syndrome (RADS) or acute-onset irritant-induced asthma is a distinct subset of irritant-induced asthma that develops in subjects without prior pulmonary disease, within 24 hours of high-level exposure to nonimmunogenic irritants such as corrosive gas, vapor, aerosol or smoke [1]. The most frequently reported agents are chlorine, toluene di-isocyanate, oxides of nitrogen and sodium hypochlorite (bleach, 40%), which is also a common agent that is widely used for indoor cleaning in rural regions [2,3]. Non-specific bronchial hyperresponsiveness is characteristic of the disease. RADS usually persists for more than a few weeks after cessation of exposure and an accurate diagnosis depends on a compatible history in the absence of any other pulmonary disorder [4,5].

For patients with RADS who require long-term pharmacologic treatment for persistant symptoms that simulate asthma (cough, wheeze and dyspea), the stepwise method as described in the asthma guidelines is followed even though it has not been formally assessed in this setting [6]. Thus, treatment failure with this approach is commonly experienced [1].

CASE PRESENTATION

We report the case of a 51-year-old female with asthma-like symptoms persisting 1 year after she had an accidental exposure to sodium hypochlorite by inhalation. Immediately after that event, she developed shortness of breath and started to cough persistently. She was subsequently hospitalized because of severe respiratory distress. One week later, she was discharged from the hospital, but noted persistent shortness of breath, cough and increased airway excitability after exposure to nonspecific stimuli such as perfume, cold air and vapor. She was then treated with aerosol bronchodilators. However, her symptoms persisted and necessitated more than 10 emergency admissions per month after severe episodes of bronchospastic responses to many various environmental stimuli. During these visits, she was diagnosed with severe asthma, and she received intermittent injections of high dose corticosteroids. She was then referred to our emergency department and hospitalized. Despite intensive treatment for over three weeks, including nebulized beta-2agonists, anti-cholinergic drugs, nebulized magnesium sulfate, oral methylpredisolone, theophylline and a leukotriene receptor-antagonist, there was no obvious improvement in her severe cough, wheeze or bronchial hyperresponsiveness.

This patient was a lifetime non-smoker, had no preexisting respiratory complaint before the exposure to sodium hypochlorite and had no prior history of allergies to drugs, foods or aeroallergens. She also developed significant adverse effects as a consequence of systemic glucocorticoid administration. She became obese (body mass index, 33.3 kg/m^2) and showed characteristics of Cushing's syndrome. She was unable to speak in complete sentences because of coughing and wheezing. Her respiratory rate was 32-breaths/min. Chest auscultation revealed a diffuse wheeze. Other physical examination findings and blood test results were normal. Her peak expiratory flow value was 330 L/min (estimated value for her age and height was 403 L/min) and oxygen saturation was 98%. For lung function tests, she

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could not complete the required 6-second expiration due to her cough reflex; therefore the test was not acceptable. Chest X-ray film, computerized tomography scan results, skin prick tests for common inhalant allergens and larynx examination for vocal cord dysfunction were normal. A diagnosis of RADS was established based on the history and laboratory findings.

The worsening of the patient's clinical situation and secondary effects of steroid use necessitated steroid-sparing treatment. We observed her episodes of bronchial hypersensitiveness after nonspecific stimuli (such as deep breath, odors, cold and stress) began with an unpreventable severe cough reflex followed by a severe bronchoconstriction. We then attempted to suppress her cough reflex with the inhalation of a local anesthetic agent, lidocaine. Written informed consent was obtained from patient.

The patient's weight was 80 kg and a dose of 5 mg/kg nebulized lidocaine was administered. Four times daily, 5 mL of a 2% injectable lidocaine solution without preservatives was introduced 1 hour before meals to prevent possible aspiration resulting from oral and pharyngeal hypoesthesia. Her symptoms such as wheezing or cough dramatically improved following this treatment. After 2 weeks of treatment, the patient was able to reduce oral steroids and discontinue the drugs, and the effects secondary to exogenous hypercortisolism decreased. Subsequently, we reduced the dosage of lidocaine, and continued her treatment with a 2% lidocaine pump spray on demand. She was discharged from the hospital and after 2 years of follow-up, she is asymptomatic with no emergency room visits since she was discharged.

DISCUSSION

The approved treatment for patients with established RADS is not different from that of any other asthmatic; preventive measures for further accidental high-level irritant exposure are also suggested [5]. However, an asthma-like therapeutic approach to this syndrome may be inadequate in some persistent cases. In addition to relieving symptoms with bronchodilators, the treatment should be given to reduce the nonspecific bronchial responsiveness. Therefore, we suggest that a local anesthetic agent may suppress the neurogenic inflammation and reflex bronchial hyperactivity.

Lidocaine is a common local anesthetic that is frequently nebulized during bronchoscopy procedures. Nebulized lidocaine is an effective and safe therapy in subjects with refractory cough and mild-to-moderate asthma in adults and children [7,8]. Hunt and colleagues demonstrated in a randomized placebo-controlled study that nebulized lidocaine is a useful anti-inflammatory asthma treatment and it may even be an alternative to glucocorticoids. However, previous studies suggest that lidocaine produces an initial reflex-mediated bronchoconstriction in patients with asthma and hyperirritable airways. Thus, caution is needed especially for its first use [9]. We also recommended to our patient not to eat or drink for 1 hour after nebulization because of its anesthetic effect. Lidocaine toxicity occurs only when serum levels exceed 5 to 6 µg/mL, and it includes lightheadedness, tremors, hallucinations, muscle twitching, seizures, arrhythmias, paresthesias and respiratory arrest [7,10]. Patients with hepatic disease should be monitored closely because of decreased drug metabolism and elimination rates. A generally accepted safe range of nebulized lidocaine is between 100 and 200 mg per dose [10].

To our knowledge, the case described in this article is the first reported case of RADS where symptom relief is obtained using nebulized lidocaine. In conclusion, nebulized lidocaine was well tolerated in our patient and could be a useful alternative for patients with RADS. This observation merits further studies to confirm the benefits of lidocaine for this group of patients, to better define other possible adverse effects and to obtain a possible place in routine treatment of RADS.

Author Contributions: Concept - L.P.O., A.E., E.K.; Desing - G.O, T.Ç, E.K, F.E.; Supervision - G.O., F.E.; Data Collection and/or Processing - T.Ç.; Analysis and/or Interpretation - T.Ç.; Literature Review - L.P.O., E.K., A.E.; Writer - L.P.O., A.E.; Critical Review - G.O, E.K., F.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

Severe Pneumonia Treated Succesfully with Levofloxacin and Oseltamivir During Flu Epidemic

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Abstract

Viral pneumonia is an important cause of community acquired pneumonias (CAP). It's not only specific to childhood period. Although immunocompromised adults are susceptible; all young and healthy adults are at risk. Viral pneumonias are usually underestimated due to lack of diagnostic modalities so a clinician must be aware of. Co-infection of viruses and bacteria is not uncommon and can be mortal especially in a flu epidemic, therefore, in the absence of diagnostic tools initiating to anti-viral treatment without delay is important.

KEYWORDS: Bronchopneumonia, epidemiology, oseltamivir

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INTRODUCTION

CAP could be mortal especially in elder patients with co morbidities. It is diagnosed in adults approximately 5.16 to 6.11 cases per 1000 persons per year [1]. According to World Health Organization (WHO) data, 450 million pneumonia cases occur per year and have %7 mortality incidence increasing by age [2]. Although lower airways are sterile, lungs are infected by aspiration of microorganisms that colonize in upper airways. Development of pneumonia depends on host defence, existence of chronic diseases, age and virulence of microorganism [3].

Bacteria, viruses, fungi and parasites are all responsible pathogens for pneumonia. Viral pneumonia accounts for 13-50% of single pathogen diagnosed CAP cases and 8-27% of mixed bacterial-viral pneumonia [4].

Diagnostic methods for viral pneumonia are limited and are not used widely thus clinical differences from bacterial pneumonia must be considered. Constitutional symptoms and atypical radiological involvement are common clues. Non-productive cough, fever, myalgia, headache are main symptoms developing slowly. In the influenza period, viruses should be remembered in the first rank as a causative agent of pneumonia. Delay to start anti-viral treatment can cause respiratory failure.

Influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, coronavirus, rhinovirus are main viral pathogens for community-acquired viral pneumonia. Influenza type A is usually the most virulent pathogen and responsible for epidemics by antigenic drift [5]. Diagnostic methods for viruses are various such as viral culture, cytological evaluation, rapid antigen detection and gene amplification. However these are not always available.

We report two cases of severe pneumonia without any immunosuppressive medical condition treated with levofloxacin and oseltamivir in an epidemic period.

CASE PRESENTATION

Case 1

A 42-years-old man without any medical history admitted to our hospital with severe fatigue, myalgia, and headache. Nearly ten days ago he had admitted to his family physician with non-productive cough and fever. Aminopenicillins-clavulanic acid and ibuprofen-pseudoephedrine were prescribed. At the third day of this treatment complaints of abdominal pain, anorexia and headache were also added.

Case 2

A 42 years woman was admitted to emergency department with shortness of breath and cough. She had symptoms for about five days. She had used ibuprofen-pseudoephedrine and vitamin C tablets without a prescription. About ten days

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ago she was complaining for upper respiratory tract infection symptoms. There was no hospital admission or antibiotic use. She had myalgia and anorexia also.

Both patients were not using any regular medication for any of chronic disease.

Their clinical and demographic features were summarized in Table 1. As shown in Table 2 infection parameters were high before treatment and were in normal ranges after treatment. Case 1 had mild thrombocytopenia without bleeding.

Patients' sputum culture, microscopy and blood culture were unremarkable. Sputum was negative for Acid resistant bacillus (ARB) and mycobacterium tuberculosis complex wasn't detected in culture.

In case 1 chest radiograph revealed bilateral heterogeneous infiltration from top to lower zone of lung (Figure 1A) and in case 2 infiltrations had lower zone predominance (Figure 2A). Because of clinical deterioration and admission during flu pandemic period computed thorax tomography (CTT) was performed. CTT revealed multiple patchy consolidations accompanied by ground glass areas. Pleural effusion wasn't observed (Figures 1B,1C,2B,2C).

RESULT

In accordance with all these data both patients had severe pneumonia. Due to being in a flu epidemic period and existence of patchy ground glass opacities on CTT we couldn't exclude viral agents. For certain diagnosis technical facilities of laboratory like polymerase chain reaction (PCR) or antigen detection tests were insufficient in our hospital. Patients' had clinical deterioration and decrease in oxygen saturation so antiviral treatment was began without delay. They took oral 75 mg oseltamivir twice a day for ten days. Due to possibility of bacterial superinfection levofloxacin 750 mg was administered once daily for 2 weeks together with antiviral therapy. Nasal oxygen, intravenous hydration, bronchodilator and antipyretics were added as supportive treatments. On the tenth day of treatment patients' general condition was better and vital signs were normal. Within 72 hours fever response was achieved in both cases. Oxygen saturation was above 95% without oxygen inhalation, there were no need to bronchodilators and arterial blood pressure was in normal ranges without intravenous fluid replacement. After treatment inflammatory markers were within normal limits (Table 2). On the chest X-ray and CTT performed after treatment completely regression was seen consistent with patients' clinical status (Figures 1D, 1E, 1F, 2D, 2E, 2F).

DISCUSSION

Although pneumonia is treated as outpatients more often by using some scores like CURB-65 (confusion, urea, respiratory rate, blood pressure and age of 65) or PSI (pneumonia severity index) clinicians can decide to hospitalize the patient [6]. However patient's general medical condition is always important. Thus although our patients didn't have comorbidities and pneumonia scores were low they were needed to be treated in hospital. Because supplementary therapies like oxygen, intravenous hydration or bronchodilators must be added to antibiotics in viral pneumonias.

Table 1. Clinical and demographic features of patients

	Case 1	Case 2
Age/Gender	41/male	42/female
Smoking status	Smoker	Non smoker
Fever	37.8°C	37.7°C
Pulse rate	90-110/min	100-120/min
Transcutaneous oxygen	%91	%88
Chest auscultation	Bibasilar fine crackles	Bibasilar fine crackles + ronchi
Blood pressure	90/60	Normal
Sputum/Blood culture	No pathogen	No pathogen
Sputum acid-fast bacilli	Negative	Negative

Table 2. Comparison of laboratory values of patients before and after treatment

	Case 1		Case 2	
Laboratory	**Pre-treatment**	**Post treatment**	**Pre-treatment**	**Post treatment**
White blood cells	17.37/L	9.58/L	18.11/L	11.93/L
Neutrophil	15.04/L	5.51/L	14.55/L	8.63/L
Lypmhocyte	7.0/L	3.27/L	13.6/L	2.6/L
CRP	32.08 mg/dL	2.5 mg/dL	10.6 mg/dL	0.75 mg/dL
Sedimentation	105 mm/hour	32 mm/hour	73 mm/hour	8 mm/hour
Albumine	3.4 g/dL	4.1 g/dL	3.8 g/dL	4.2 g/dL
LDH	491 U/L	223 U/L	317 U/L	211 U/L
Platelets	92/L	385/L	457/L	369/L

CRP: C- reactive protein, LDH: Lactate dehydrogenase.

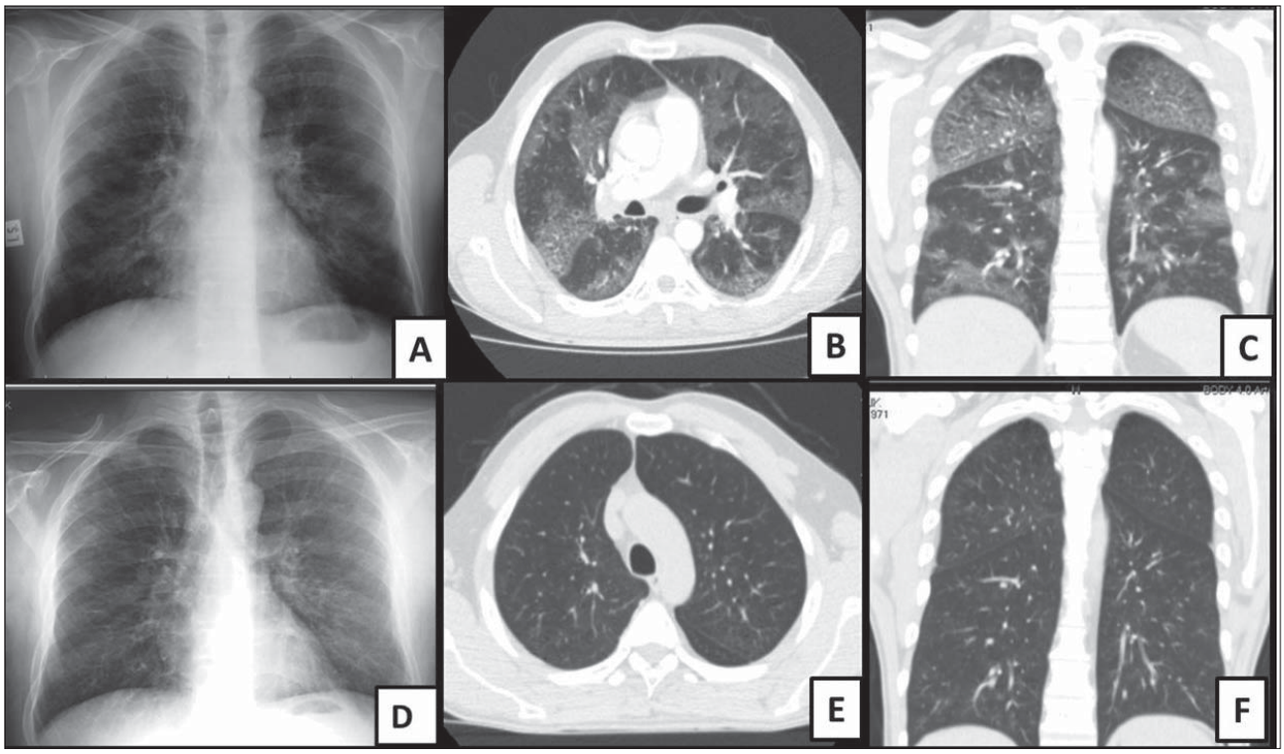

Figure 1. (A) Bilateral heterogeneous infiltration on chest X-ray. **(B, C)** Multiple patchy consolidations accompanied by ground glass areas without pleural effusion on computed thorax tomography (Case 1). **(D, E, F)**: Completely regression on chest X-ray and computed thorax tomography (Case 1).

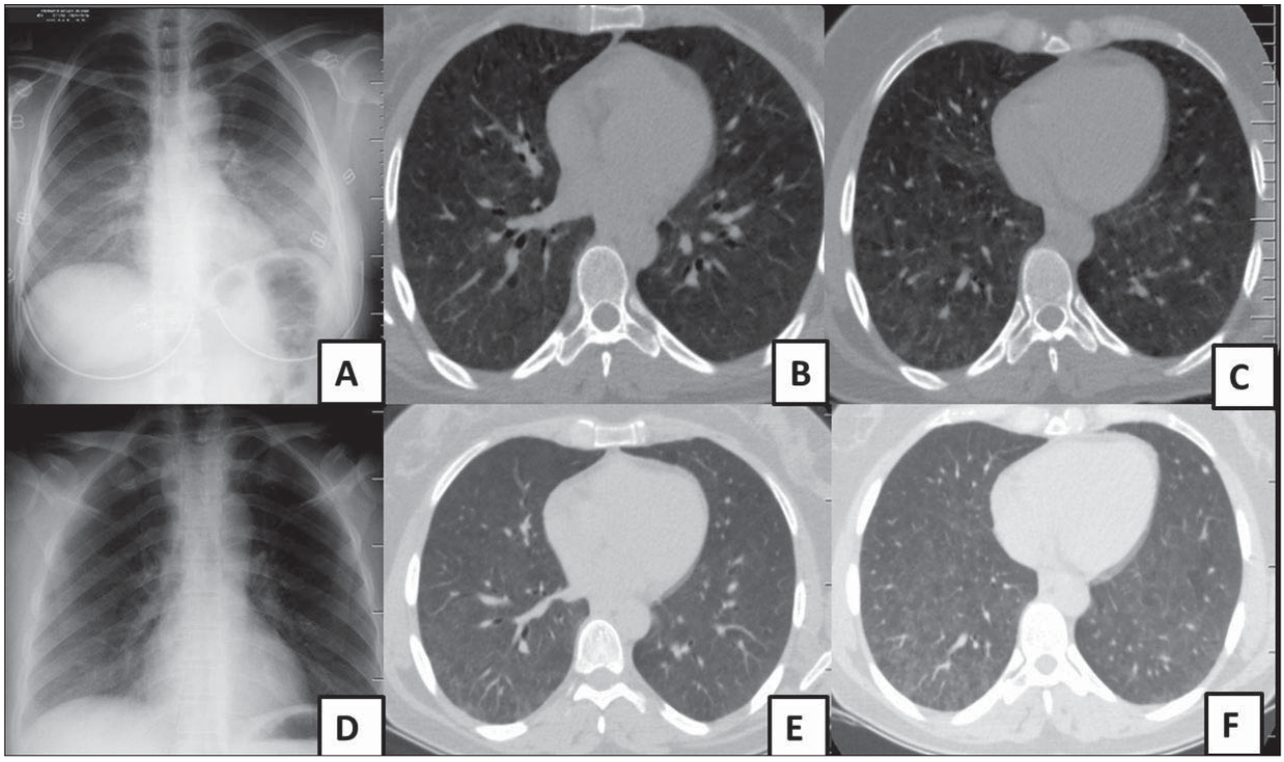

Figure 2. (A) Bilateral infiltration showing lower zone predominance on chest X-ray. **(B,C)** Multiple patchy consolidations accompanied by ground glass areas (Case 2). **(D, E, F)** Completely regression on chest X-ray and computed thorax tomography (Case 2).

Viruses like influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, coronavirus, rhinovirus constitutes %13-50 of CAP and usually occur with bacterial agents so to diagnosis purely viral pneumonia is difficult. Influenza type A and B are responsible for most of viral pneumonias especially in epidemic. It can change its' glycoprotein structure (neuraminidase and hemagglutinin) by antigenic shift and drift so that increase virulence [4,7]. To

distinguish, clinical clues and epidemiology can help the physician to consider viral agents. Constitutional symptoms are very significant. Fever, myalgia and gastrointestinal symptoms are more obvious in influenza than other viral pathogens [7]. Our patients had fever; myalgia and case one had gastrointestinal symptoms. Also our patients' inflammatory markers were high supporting to bacterial co-infection so empiric antibiotics were added to oseltamivir treatment.

Respiratory viruses damage upper airway epithelium and reach lung parenchyma by secretions or haematogenous [8]. Influenza, adenovirus and herpes group have cytopathic effects on respiratory epithelium. Influenza virus causes necrotizing bronchitis and/or bronchiolitis, inflammatory cell infiltration in alveoli and diffuse alveolar damage in severe cases. Although patchy bilateral alveolar infiltrations and interstitial involvement are common radiological findings parenchymal attenuation disturbances, nodules, micro nodules, interlobular septal thickening can be seen on CTT [9]. There were bilateral ground glass opacities and patchy infiltrates both of patients. These radiological findings can be related malignant/non-malignant reasons so they are non-specific. Broncho alveolar carcinoma is first differential diagnosis as malignancy. Our patients' symptoms were so acute and responded to therapy in ten days unlike malignancy. Hypersensitivity pneumonia and desquamative interstitial pneumonia could be considered. For these nodular opacities are expected with ground glass areas. Patients didn't have nodules on CTT also there was no risk factor or antigen exposure. If they had haemoptysis diffuse alveolar haemorrhage can be conceivable. Actually viral pneumonia which is clinically serious can cause alveolar haemorrhage. There weren't decline in haemoglobin or haemoptysis [10]. They didn't have medical history suggesting vasculitis or immunological disease. So systemic steroid wasn't added to therapy. If patients had any immunocompromised condition aspergillus could be remembered.

H5N1 and H7N9 are avian influenza and H1N1 is swine influenza responsible for pandemics and outbreaks in winter season. In June 2009, the WHO raised its pandemic alert level to the highest level because of outbreak of H1N1 influenza A virus infection [11]. In late March and April 2013, human cases of novel avian influenza A H7N9 infection in China were reported and a rise in the number of cases occurred in late 2013 and early 2014 in influenza season [12]. Both patients administered our hospital in November 2013 so influenza was susceptible.

In an epidemic period if patient is highly suspected clinically and radiologically oseltamivir should be initiated in 48 hours to prevent viral replication. 75 mg twice a day for five days is standard therapy. In severe cases or presence of clinical progression to prolong to ten days or 150 mg twice a day is applicable [13,14]. Both of our patients had administered to hospital with delay and their clinical condition wasn't good so oseltamivir were given 75 mg twice a day for 10 days. So benefit of supplementary therapies shouldn't be denied.

CONCLUSION

Viral pneumonias should be remembered as a differential diagnosis when bilateral and patchy ground glass opacities were detected on CTT and if patients' clinical status is suggestive for viral causes; physician should not hesitate to start antiviral agents immediately.

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