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Turkish Thoracic Journal
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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.

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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.

g. Video: Videos submitted for online broadcasting purposes, on the internet site of Turkish Thoracic Journal, are accepted. The video dossier should be maximum 3MB in size and in .mpeg or .vmf format.

h. Case reports should contain sections for English title, English running title, English abstract, keywords, Introduction, Case Presentation and Discussion. They should include new cases or imply clear messages. All submitted case reports will be first reviewed by the editorial committee and those that do not include new cases and/or do not imply clear messages could be rejected without sending it for arbitration.

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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EDITORIAL

Dear Colleagues,

The New Year started with extraordinary developments for the Turkish Thoracic Journal. It is our great pleasure to inform you that The Turkish Thoracic Journal is now indexed by Emerging Sources Citation Index (ESCI) of Thomson Reuters. The other good news is that we will start using Thomson Reuter's ScholarOne for online manuscript submission and peer review process soon. Thus, we believe the peer review process will be more efficient and faster, and this will also let your manuscripts to be seen widely at international platforms by your counterparts. At present, the transition procedure is on-going, and you will be able to submit your manuscripts through ScholarOne system in due course. This will be clearly indicated at the Journal's website.

In this first issue of 2016, there are research papers on "sleep disorders of young university students", "thrombocytopenia as a risk factor in intensive care unit", "smoking cessation", "endobronchial biopsy in the diagnosis of sarcoidosis" and interesting case reports, which we believe will be useful for our readers.

We wish you a very happy and productive year of 2016, and look forward to meeting you with our next issue in April 2016.

With best wishes,

Editors
Hasan Bayram
Öner Dikensoy

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ORIGINAL INVESTIGATION

Effect of Nasal Continuous Positive Airway Pressure Therapy on the Functional Respiratory Parameters and Cardiopulmonary Exercise Test in Obstructive Sleep Apnea Syndrome

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Abstract

OBJECTIVES: Nasal continuous positive airway pressure (nCPAP) treatment is the gold standard treatment for obstructive sleep apnea syndrome (OSAS). In this study, we aimed to show that the pulmonary functions, exercise limitation on the cardiopulmonary exercise test (CPET), and the health-related quality of life can be improved after a short treatment period by nCPAP.

MATERIALS AND METHODS: Our case group with severe obstructive sleep apnea (OSA) performed incremental CPET before and after 8 weeks of nCPAP treatment. All the subjects also underwent physical examination, body composition analysis, simple spirometric measurements, maximal inspiratory pressure (PImax)-maximal expiratory pressure (PEmax), and lung volume tests before and after nCPAP treatment.

RESULTS: Thirty-one patients (4 female, 27 male) completed the study. The mean age of the patients was 53.41 ± 1.46 years. Sixteen had at least one comorbidity. In addition, 17 of the subjects were ex-smokers. After nCPAP treatment for 8 weeks, higher PImax-PEmax ($p< 0.05$), peak oxygen uptake ($p= 0.001$), workpeak ($p= 0.000$), maximal heart rates ($p= 0.000$), and short form-36 scores ($p< 0.05$) were observed. nCPAP treatment helped control the blood pressure ($p= 0.005$). There was no significant change in body composition analysis, spirometric parameters, and lung volumes.

CONCLUSION: In a short time period, nCPAP can improve exercise capacity, respiratory muscle strength, and the health-related quality of life scores and help control blood pressure.

KEY WORDS: Obstructive sleep apnea syndrome, cardiopulmonary exercise test, nasal continuous positive airway pressure, peak oxygen uptake, short form 36

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by total (apnea) or partial (hypopnea) repetitive upper airway obstruction resulting in oxygen desaturation, an awakening of sleep, loud snoring, and increased daytime sleepiness [1,2]. Sympathetic activation, vascular endothelial dysfunction, metabolic disorders, oxidative stress related to cyclic intermittent hypoxia, and inflammation may lead to cardiovascular diseases existing in OSAS [3,4]. Several studies have shown that OSA and chronic heart failure, hypertension, and obesity are linked to each other [5,6]. Pulmonary functions of OSAS have been explored in recent years [7-9]. The most commonly known spirometric findings in OSAS are that forced expiratory flow at 50%/forced inspiratory flow at 50% (FEF_{50}/FIF_{50}) > 1 and a saw-tooth pattern in the flow-volume curve [7-10]. Overweight OSA patients may have abnormal lung function values because of their weight. These include decreases in total lung capacity (TLC) and functional residual capacity (FRC) due to mainly a decrease in the expiratory reserve volume (ERV) and a decrease in the compliance of the respiratory system [11,12]. High body mass effects metabolic energy during exercise, resulting in ventilatory stress. Daytime hypersomnolence, low daily activity, and tissue hypoxemia impairs muscle function, which affects exercise fitness. It has been shown that the exercise limitation is related to the severity of sleep disorders independent of body habitus [12]. Decreases in cardiovascular mortality and non-fatal cardiovascular events have been shown in long-term follow-up studies of OSA patients under continuous positive airway pressure (CPAP) treatment [13].

It was presented at; 1-European Respiratory Society Annual Congress 2012; 2. WORLD ASSOCIATION OF SLEEP MEDICINE - 5th World Congress on Sleep Medicine; 2-Turkish Thoracic Society Annual Congress 2012; 4. Turkish Sleep Medicine Society Annual Congress 2012

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A meta-analysis about the CPAP effects on the quality of life in OSAS showed little impact of CPAP on the general quality of life when compared with control treatment. This meta-analysis also showed that generic quality of life instruments might not find the considerable changes in OSAS. CPAP did not improve general quality of life scores but improved physical domains and vitality [14].

Cardiopulmonary exercise testing (CPET) is used to differentiate the etiology of exercise limitation as follows: cardiac, pulmonary, or resulting from muscle dysfunction [15-19]. Previous studies evaluating exercise limitation in OSA have shown improvements in cardiac dysfunction and CPET performance after 8 weeks of nasal CPAP (nCPAP) treatment [20].

Nasal continuous positive airway pressure treatment effects on CPET in OSAS have been studied with only 20 patients in one study [20]. The aim of our study was to support the improvement in exercise limitation in OSA patients after a short-term nCPAP treatment period. We tried to determine whether pulmonary functions and health-related quality of life can also be improved after 60 days of nCPAP treatment using a larger study group.

MATERIALS AND METHODS

Subjects

Study protocols and written informed consents of the patients were approved by the institutional review committee on clinical research of the Dokuz Eylül University Faculty of Medicine, Turkey. Patients selected from those whose polysomnography reports were compatible with moderate or severe OSAS and who underwent nCPAP titration study prior to enrolment. The inclusion criteria for this study included patients who were non-smokers or ex-smokers for at least 12 months. Medical conditions that would affect pulmonary function tests and make exercise dangerous, such as chronic obstructive pulmonary disease, asthma, lung cancer, bronchiectasis, angina pectoris, congestive heart failure, poorly controlled diabetes mellitus, or other metabolic diseases, recent upper respiratory surgery, acute infection within 6 weeks prior to the study, morbid obesity, and anemia served as exclusion criteria. We also added neurological, psychological, and cooperation problems that would affect good participation to the exclusion criteria.

Participants underwent physical examination, body composition analysis, pulmonary function testing, CPET, and completed the general health-related quality of life questionnaires before and after nCPAP therapy. Patients did not have any instruction on diet, exercise, or weight loss during this period.

Physical Examination

Cardiac and pulmonary examinations were performed at baseline, including manual blood pressure measurements taken at rest (Riester Minimus III 0124).

Short Form-36 (SF-36) Health Survey

The general health-related quality of life was evaluated using the SF-36 questionnaire. SF-36 has eight multi-item dimensions that have scores from 0 to 100: physical functioning, physical role (role limitations due to physical problems), vitality, social functioning, emotional role (role limitation due to emotional problems), body pain, general health, and mental health.

Body Composition Analysis

Body mass index (BMI), percent body fat (PBF), and waist-to-height ratio (WHR) were calculated by bioelectrical impedance analysis (BIA) [21]. The technology assigns the electrical impedance of body tissues, which provides an estimate of total body water (TBW) [21]. Using values of TBW derived from BIA, one can then estimate fat-free mass (FFM) and body fat (adiposity) [21]. The availability of BIA in general adults and obese adults has been shown by several studies [22-25]. In our study, we used a BIA device with eight tactile electrodes (InBody720, Biospace, GE Health Care, Madison, USA), which is not suitable for pregnant subjects and those with a prosthesis. All of the subjects were advised to fast for 2 h prior to the testing.

Pulmonary Function Tests

The study group performed pulmonary function tests to determine the lung functions. Spirometry and respiratory muscle strength mouth pressures were administered with a Sensor medics Vmax 22 machine (SensorMedics Inc., Anaheim, CA, USA) confirming to the ATS/ERS criteria [26,27]. Forced vital capacity (FVC), first second forced expiratory volume (FEV_1), FEV_1/FVC, forced expiratory flow at the 25% point to the 75% point of forced vital capacity (FEF_{25-75}), and forced expiratory flow at 50% (FEF_{50}) values were measured. Body plethysmography (Jaeger Master Screen Body Spirometry V 5.1.0, Germany) was used to measure the lung volume. Residual volume (RV), total lung capacity (TLC), RV/TLC, inspiratory capacity (IC), inspiratory reserve volume (IRV), and expiratory reserve volume (ERV) were recorded.

Exercise Testing

Exercise tests were performed by an electrically braked cycle ergometer (Ergoline GmbH via Sprint 150 P Master Screen Cpx Ergospirometry V 5.11.0). A physician monitored the electrocardiographic changes. Serious cardiac arrhythmias, hypotension, and electrocardiographic changes by maximal incremental cycle ergometry protocols were the defined criteria for stopping. This incremental cycle ergometry protocol consists of 3 min of rest, followed by 3 min of unloaded pedaling with incremental loading (3 w per 10 s) until reaching a maximal load [28]. Terminating criteria for exercise testing were the patient reaching volitional exhaustion or the physician terminating the test. We evaluated the pre-test and post-test dyspnea severity and leg tiredness with a modified Borg scale.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) ver. 15 software package. We used the Wilcoxon signed rank test to compare the pre- and post-treatment data of the study group. All the values were calculated as the mean ± standard

deviation. We used the Kruskal–Wallis test to determine the correlation between the changes in BMI and changes in the CPET parameters. This was a per protocol analysis, and those subjects who completed the test were added in the analysis.

RESULTS

Forty patients consented to the study, of whom 31 completed all the baseline and follow-up testing. The subjects were contacted by telephone every 2 weeks to determine compliance and to identify problems with CPAP therapy use. CPAP therapy for an average of 4 h a night for at least 70% of the nights was considered as CPAP compliance. We checked the effective CPAP treatment with smart cards in patients' CPAP machines after 8 weeks. Nine patients did not meet the criteria for compliance due to removing the CPAP early in the night. When patients first started using the CPAP, they established their pattern of compliance within the first week of treatment.

Characteristics of the Subjects

There were 31 subjects (4 females and 27 males), with a mean age of 53.4 ± 1.4 years. Sixteen of the patients had hypertension and/or diabetes mellitus. In addition, 17 of the patients were ex-smokers, and the ex-smokers' mean package year was 18.05 ± 2.46. The mean AHI of the subjects was 54.25 ± 3.65, the lowest oxygen saturation was 75.29 ± 1.74, and the oxygen desaturation index was 47.26 ± 3.70 per hour. The mean CPAP pressure was 7.93 ± 0.34. Most of the study population (90%) was composed of patients with a BMI higher than 25 kg/m^2 but lower than 40 kg/m^2.

Physical Examination and Body Composition Analysis

These are summarized in Table 1. None of the patients had pathological diagnosis during the 8 weeks of nCPAP treatment. The mean systolic and diastolic blood pressures decreased after nCPAP treatment. There were no significant changes in neck circumference, BMI, PBF, or WHR after nCPAP treatment.

Quality of Life

In our study group, nCPAP treatment led to significant improvements in the SF-36 health survey. Patients undergoing 8 weeks of nCPAP treatment scored better in physical function, physical problems, general health, energy vitality, social functioning, emotional problems, mental health, physical component summary, and mental component summaries (Table 2). There was no significant change in body pain (Table 2).

Table 1. Physical examination and body composition analysis

	Before CPAP	After CPAP	p
Mean systolic BP	122.26 ± 1.2	118.39 ± 1.3	0.005
Mean diastolic BP	78.70 ± 0.6	76.12 ± 1.1	0.021
Neck circumference	39.53 ± 0.5	39.50 ± 0.5	0.317
BMI	31.43 ± 0.8	31.74 ± 0.7	0.090
PBF	32.50 ± 1.3	33.40 ± 1.3	0.051
WHR	0.97 ± 0.01	0.92 ± 0.04	0.061

Data are presented as mean ± SD. Wilcoxon signed rank test was used. BP: blood pressure; BMI: body mass index; PBF: body fat percentage; WHR: waist-to-hip ratio.

Pulmonary Function Tests and Lung Volumes

After the nCPAP treatment, there were no significant changes in all of the pulmonary function tests and lung volumes except FEV_1 (%). PI max and PI max values were better after treatment (Table 3).

Table 2. Quality of life

	Before CPAP	After CPAP	p
Body pain	76.4 ± 5.1	84.3 ± 3.6	0.145
General health	54.2 ± 3.3	71.3 ± 3.1	0.000
Energy vitality	54.7 ± 4.5	78.1 ± 2.8	0.000
Social functioning	54.2 ± 3.3	71.3 ± 3.0	0.000
Emotional problems	49.4 ± 7.6	79.9 ± 6.7	0.000
Mental health	66.7 ± 2.9	77.4 ± 2.6	0.000
PCS	45.9 ± 1.5	51.8 ± 1.3	0.004
MCS	43.2 ± 1.8	53.8 ± 1.2	0.008
Physical function	77.6 ± 3.8	86.8 ± 3.8	0.001
Physical problems	51.7 ± 7.8	93.3 ± 4.1	0.000

Data are presented as mean ± SD. Wilcoxon signed rank test was used. PCS: physical component summary; MCS: mental component summary.

Table 3. Spirometric measurements

	Before CPAP	After CPAP	p
FVC (% pred.)	96.1 ± 2.5	94.6 ± 2.6	0.294
FEV_1 (% pred.)	99.9 ± 2.5	97.2 ± 2.5	0.017
FEV_1 / FVC	84.3 ± 0.8	83.1 ± 0.9	0.157
PEF (% pred.)	99.8 ± 3.4	98.2 ± 3.1	0.468
FEF_{50} (% pred.)	99.9 ± 4.2	94.7 ± 4.4	0.112
FEF_{25-75} (% pred.)	88.3 ± 3.9	91.8 ± 4.5	0.491
FEF_{50}/FIF_{50}	1.5 ± 0.1	1.3 ± 0.1	0.176
PI max	74.6 ± 5.1	82.0 ± 5.9	0.011
PE max	98.2 ± 5.7	109.3 ± 6.7	0.009
RV (% pred.)	109.4 ± 5.5	103.1 ± 4.6	0.710
TLC (% pred.)	96.4 ± 2.4	93.0 ± 2.4	0.252
IC (% pred.)	94.7 ± 4.5	96.5 ± 4.3	0.389
ERV (% pred.)	87.8 ± 10.9	79.1 ± 8.5	0.272

Data are presented as mean ± SD. Wilcoxon signed rank test was used. FVC: forced vital capacity; FEV_1: forced expiratory volume; PEF: peak expiratory flow; FEF_{50}: forced expiratory flow at 50%; FEF_{25-75}: forced expiratory flow at 25-75%; FIF_{50}: forced inspiratory flow at 50%; PI max: maximal inspiratory pressure; PE max: maximal expiratory pressure; RV: residual volume; TLC: total lung volume; IC: inspiratory capacity; ERV: expiratory reserve volume.

Table 4. Cardiopulmonary exercise test (CPET) results

	Before CPAP	After CPAP	p
VO_2 peak (%)	61.0 ± 2.2	68.6 ± 2.2	0.001
Workpeak (W)	109.6 ± 4.5	126.5 ± 4.5	0.000
Maximal hearth rate	129.5 ± 3.0	136.2 ± 3.0	0.000
Hearth rate reserve	36.4 ± 2.6	29.6 ± 2.4	0.000
SpO_2 (%)	96.7 ± 0.2	97.3 ± 0.1	0.003
O_2 pulse (%)	69.2 ± 2.6	76.5 ± 2.9	0.019
VE max (L/dk)	53.1 ± 2.4	63.4 ± 2.9	0.000
Breathing reserve (%)	52.1 ± 2.2	41.8 ± 2.2	0.000

Data are presented as mean ± SD. Wilcoxon signed rank test was used. VO_2 peak: peak oxygen uptake; SpO_2: blood oxygen level O_2; pulse: pulse oximetry; VE max: maximal pulmonary ventilation.

Exercise Tests

Dyspnea and leg fatigue severity of patients was lower after the 8 weeks of nCPAP treatment. Significant improvements in VO_2 peak, maximal work peak, maximal heart rate, oxygen saturation (SpO_2), oxygen (O_2) pulse, maximal minute ventilation (VE max), and correlation of a decrease in heart rate reserve with the increase in the maximal heart rate were noted on exercise testing after nCPAP treatment (Table 4).

DISCUSSION

In our study, severe OSA patients had lower VO_2 peak, workpeak, maximal heart rate, and oxygen pulse, all of which improved after a short time with nCPAP treatment period. There was no significant improvement in the respiratory parameters, but the quality of life scores were significantly better after treatment.

During the treatment period, study patients did not receive any instruction on diet, exercise, or weight loss. Patients' anthropometric measurements after the treatment period did not change significantly. Therefore, improvements may be related to nCPAP treatment. We found that nCPAP treatment helped control arterial blood pressure and improved the inspiratory and expiratory muscle functions and quality of life scores.

Ozturk et al. [15] showed that moderate-to-severe OSA patients had limited exercise capacity. They determined that this exercise limitation seemed to originate from cardiovascular reasons and/or peripheral vascular impairment. Aguillard et al. [22] had to end their moderate and severe OSA patients' CPET because of tiredness. They said that the subjective tiredness was not correlated with OSA severity. Daytime hypersomnolence may be a reason for exercise limitation in OSA patients.

In our study, all the patients tolerated CPET without any serious complications such as ischemia or arrhythmias in the echocardiogram. They stopped exercising at submaximal ventilation. The reasons for stopping CPET were dyspnea and leg muscle tiredness.

Our patients had a small but significant improvement in their blood pressure; similar findings were reported by Lin et al. [20]. In both studies, patients' exercise responses after nCPAP treatment were better without any significant differences in age, BMI, or exercise habits. These changes seem to be related with only nCPAP treatment. In our study, we found significant increases in maximal heart rate and SpO_2. The increases in maximal heart rate and breathing reserve may show that the patients did better exercise after nCPAP treatment. Increases in VE max may be related with the increase in workpeak. The increase in SpO_2 after nCPAP treatment supports the improvement in exercise capacity. The potential reason for this is the sleep recovery because sleep restores cellular functions in the brain and the muscles [29,30]. The rise in tissue oxygenation may be the reason for the higher SpO_2.

Kaneko et al. [31] showed that CPAP treatment helped control systolic blood pressure and increased the left ventricular ejection fraction. Doherty et al. [32] found that long-term CPAP treatment decreased the cardiovascular mortality without any effect of age, BMI, smoking, alcohol, or OSA severity. In our study, the improvements in O_2 pulse, maximal heart rate, and arterial blood pressure may show the cardiovascular recovery in OSA patients. There was no significant difference in exercise capacities between obese and non-obese patients before nCPAP treatment. This may support the idea that obesity does not have an important effect on exercise limitation in OSA patients.

Inspiratory muscles of OSA patients are under more negative intrathoracic pressure compared with healthy subjects [33]. Aran et al. [34] showed that the respiratory muscle force and resistance were lower with night-time CPAP treatment in OSA patients. Barreiro et al. [35] noted that night-time inspiratory muscle resistance and continuous hypoxia-reoxygenation circle may increase the oxidative stress in respiratory muscles, and CPAP treatment may recover this respiratory muscle dysfunction. In our study group, inspiratory and expiratory muscle strength improved significantly after 8 weeks of nCPAP treatment. Recovery of respiratory muscle resistance and oxidative stress in muscles after CPAP treatment may be the reason. Bonay et al. [36] showed there was no change in TLC and RV in OSA patients without obstructive pulmonary disease in their study when they observed pulmonary functions before and after nCPAP treatment in OSA patients with and without obstructive pulmonary disease. In accordance with the literature, there was no significant difference in lung volumes (TLC, RV, IC, ERV) in our study after the treatment.

There was no change in spirometric measurements except FEV_1, but this was not clinically important or meaningful. Our patients did not have any different treatment that could influence their spirometric parameters. The reason for FEV_1 loss in our study patients is not clear. Bonay et al. [36] noted a loss of FEV_1 and FEF_{25-75} in OSA patients without obstructive lung disease after 16.8 ± 8 months of nCPAP treatment. Chaouat et al. [37] detected a decrease in FEV_1 after nCPAP treatment (64 ± 6 months) related to a high smoking history

(77%). Bonay et al. [36] noted that CPAP may irritate airway epithelia and induce airway inflammation. In addition, long-term nCPAP may act as a mechanical alteration of the nasal mucosa and creates a change in small airway resistance via the nasobronchial reflex. In our study, we did not think the mechanical effect of CPAP was the cause for the FEV_1 loss because of the short-term follow-up period. Our patients used their CPAPs in cold winter days, and most of the machines did not have any heater plate. Cold air inhalation might cause bronchoconstriction and increase mucus secretion.

A meta-analysis about the effect on the quality of life of CPAP in OSAS showed little impact of CPAP on the general quality of life when comparing CPAP with a control treatment. This meta-analysis also showed that generic quality of life instruments might not be suitable for detecting changes in the quality of life in OSA patients and that CPAP did not improve the general quality of life scores but did improve the physical domains and vitality. In our study, we found significant improvements in physical function, physical problems, energy/vitality, social functioning, emotional problems, mental health, physical component summary, and mental component summary scores after nCPAP treatment. SF-36 may be useful for discriminating patients with and without OSAS and may be sensitive to treatment-induced changes [14].

Our study is limited by the small sample size and lack of a control polysomnography after nCPAP treatment. Because of the known effects of smoking on the respiratory system, active smokers and those who have recently quit smoking were excluded. Morbidly obese OSA patients were not included in our study because they could not finish exercise testing. These are the reasons for our small sample size. However, our study numbers were greater than in other similar studies. Our patients could not undergo control polysomnography because some of them did not want to spend one more night in the hospital. In further studies, it will be better to perform control polysomnography after an nCPAP treatment period to show the change in desaturation time or percentage during sleep. If the desaturation period is shorter after treatment, this will help to explain the recovery of tissue oxygenation and exercise capacity.

In conclusion, nCPAP treatment is effective in reducing exercise limitation, can help control blood pressure, and improves respiratory muscle strength. nCPAP can also improve the quality of life scores in OSA patients without any uncontrolled comorbidities.

Ethics Committee Approval: Institutional review committee on non-invasive clinical research of the Dokuz Eylül University School of Medicine (22.09.2010).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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ORIGINAL INVESTIGATION

Thrombocytopenia: A Risk Factor of Mortality for Patients with Sepsis in the Intensive Care Unit

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Abstract

OBJECTIVES: The objective of this study was to evaluate the intensive care unit (ICU) and long-term mortality in sepsis patients with/without thrombocytopenia on the fifth day of ICU admission.

MATERIALS AND METHODS: The retrospective observational cohort study was performed in a teaching hospital, and patients with sepsis who stayed more than 4 days in the ICU between January 2012 and December 2012 were included. Patients were divided into two groups according to thier platelet count at fifth day of ICU stay: Group 1, < 150.000/µL; Group 2, >150.000/µL. Patients having thrombocytopenia on admission were excluded. The patients' characteristics, comorbid diseases, body mass index, arterial blood gas analysis and blood biochemistry results, SIRS criteria, Acute Physiological and Chronic Health Evaluation Score II (APACHE II), implication of invasive and non-invasive mechanical ventilation, use of sedation, nutrition information, and culture results of microbiological samples were recorded. The groups were compared according to the recorded data. Logistic regression analysis was performed for ICU mortality; the Kaplan–Meier test was used to evaluate 12-month survival after ICU discharge.

RESULTS: During the period, 1003 patients were admitted to the ICU; 307 sepsis patients were included in the study. Group 1 (n= 67) and Group 2 (n=240) had similar patient characteristics and sepsis findings. The groups had similar ICU and hospital stays; mortality was higher in Group 1 than in Group 2 (40.3% vs. 17.5%, respectively, p< 0.001). Fifth day thrombocytopenia, septic shock, male gender, and low albumin levels were found to be risk factors of ICU mortality; the respective odds ratios, 95% confidence intervals, and p values for these factors were 3.03, [1.15-7.45], p= 0.025; 4.97, [1.79-13.86], p= 0.002; 3.61, [1.27-10.23], p= 0.001; and 0.19, [0.07-0.52], p= 0.001. Follow-up after a year indicated that 124 out of 238 (52.1%) patients died, and 50% of the deaths occurred in the first 2 months. Kaplan-Meier analysis revealed no statistically significant effects of thrombocytopenia at ICU day 5 on 12-month mortality after ICU discharge.

CONCLUSION: Higher rates of septic shock and mortality were seen in sepsis patients with thrombocytopenia in the ICU. The measurement of thrombocytopenia in the ICU, which is easy and low-cost, may help to predict mortality. Thus, precautions can be taken early in patient treatment and follow-up. As we know, early intervention is crucial in the approach to sepsis.

KEY WORDS: Thrombocytopenia, sepsis, mortality, intensive care unit

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INTRODUCTION

Various immunological changes induced by mediators involved in the pathogenesis of sepsis lead to organ failure and subsequent organ dysfunction. Once circulatory failure and shock have developed, the mortality rate among patients with severe sepsis increases to > 50% [1]. As an indicator of hematological system failure, thrombocytopenia reflects an increase in the mortality rate and severity of sepsis; therefore, it is included in the Sepsis-related Organ Failure Assessment (SOFA) score [2]. A limited number of studies have evaluated the relationship between sepsis and reduction in platelet count despite the fact that thrombocytopenia is equally as important as circulatory failure [3,4].

Determination of the most appropriate therapeutic agent and rapid initiation of treatment allow for the reversal of the damage that occurs during early pathogenesis. Because the causative microorganism cannot be identified in approximately half of the patients with sepsis, treatment is directed at developing organ failure. Although improvement in the treatment of patients with sepsis was ensured by the Surviving Sepsis Campaign and other published guidelines, thrombocytopenia remains a major problem for these patients in the ICU [5]. Few studies have

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investigated survival during and after an ICU stay among patients with sepsis and the worsening of thrombocytopenia with the passage of time post-admission [6,7].

In the present study, we hypothesized that the development of thrombocytopenia due to sepsis, particularly on day 5 of hospitalization, may be associated with a worse prognosis of patients in the ICU and after ICU discharge than in non-thrombocytopenic patients with sepsis.

MATERIALS AND METHODS

This study was approved by the Internal Review Board of Kartal Lütfi Kırdar Teaching Hospital-İstanbul. It was conducted in accordance with the ethical principles stated in the Declaration of Helsinki [8]. This retrospective cohort study was performed in a 22-bed respiratory ICU of a single tertiary training and research hospital. All patients were followed up by the same pulmonary specialist team (n= 8) from 1 January 2012 to 31 December 2012.

Patients

All patients with sepsis who were admitted to our ICU and stayed more than 4 days were enrolled in the study. Patients having thrombocytopenia on admission were excluded. All patients had pulmonary-origin sepsis (pneumonia, infective bronchitis, bronchiectasis, and other conditions). It is known that in heparin-induced thrombocytopenia (HIT), the platelet count usually falls 5-14 days after heparin is first administered. To exclude HIT, patients were stratified into two groups according to their fifth day thrombocyte count. Group 1 comprised patients with a thrombocyte count of ≤ 150,000/mL or that had decreased to ≥ 50% of the ICU admission count on their fifth day in the ICU. Group 2 comprised patients with a thrombocyte count of > 150.000 or that had decreased by < 50% of the ICU admission count on their fifth day in the ICU.

Definitions

The systemic inflammatory response syndrome (SIRS) criteria were defined as follows:

- Core body temperature of > 38°C or < 36°C,
- Heart rate of ≥ 90 bpm,
- Respiratory rate of ≥ 20/min (or $PaCO_2$ of < 32 mmHg),
- White blood cell count of ≥ 12.000/μL or ≤ 4000/μL or > 10% immature forms.

Sepsis was defined as the presence of at least two SIRS criteria [9] caused by a known or suspected infection. Patients with organ dysfunction and/or hypoperfusion abnormalities were considered to have severe sepsis. Shock was defined as the need for vasoactive drugs (> 5 μg/kg/min of dopamine, dobutamine, or norepinephrine at any dose) for at least 1 h [9]. Septic shock was diagnosed when shock was associated with a documented or assumed infection without any other identifiable cause of shock [9].

Data Collection

The pre-ICU locations and date of ICU admission were recorded for all patients. Demographic data, comorbid diseases (diabetes, cardiovascular disease, chronic renal disease, and chronic respiratory disease), body mass index (BMI, kg/m^2), arterial blood gas analysis and blood biochemistry results, SIRS criteria [9], APACHE II [10], and other ICU outcomes (implication for and durations of invasive and non-invasive mechanical ventilation, lengths of ICU and post-ICU hospital stay, use of sedation, and nutrition information) were gathered from the patients' ICU files. Hemogram parameters, including thrombocyte levels, white blood cell levels, hemoglobin levels, biochemical blood analysis results, activated partial thromboplastin time, and international normalized ratio, were noted on days 1 and 5 of ICU admission. All agents isolated from culture samples were documented. All patients were treated according to established guidelines [11].

We followed the Modified Protocol for Surviving Sepsis [3] and Early Directed Goal Therapy protocol [12]. Invasive mechanical ventilation (IMV) with a moderate tidal volume [13] was performed if the patient was unresponsive to or had a contraindication for non-invasive mechanical ventilation (NIMV) [14]. Moderate-dose steroids [15] were administered at 20 mg three times daily for 7 days in patients without contraindications. A glucose control protocol [16] was followed to maintain blood glucose levels between 110 and 140 mg/dL (< 150 mg/dL). A sedation protocol was applied during mechanical ventilation. The Richmond Agitation-Sedation Scale was used for the determination of infusions and assessment of the daily need for sedation [17].

Microbiology

Bronchial secretions were collected via deep tracheal aspiration in intubated patients. Sputum was collected in a sputum Petri dish in non-intubated patients. A blood culture was obtained and incubated in aerobic culture media in patients with hyperthermia or hypothermia (< 36°C or > 38°C, respectively).

Statistical Analysis

Descriptive statistics were used to define the characteristics of the study population. All recorded data were compared between the two groups. We further divided the patients with severe sepsis into two subgroups according to mortality. Data were compared using the Mann-Whitney U test and Student's t-test for nonparametric and parametric variables, respectively. All nonparametric values are presented as median with interquartile range (25%-75%). We used the chi-square test to compare categorical variables (sex, comorbidities, and IMV and NIMV status) between the two groups.

Logistic regression analysis was performed to evaluate the multivariate associations between risk factors and mortality. The multivariate model was adjusted for baseline severity (SOFA score on admission to the ICU). Odds ratios, 95% confidence intervals, and p values were reported. Patients were followed for 12 months after ICU discharge, and mortality status was recorded during this period. The long-term survival analysis of the two groups after ICU discharge according to the fifth day of thrombocytopenia was analyzed using the Kaplan-Meier curve. Data were analyzed using the Statistical Package for the Social Sciences 15.0 (SPSS, Inc., Chicago, IL, USA). A p value of < 0.05 was considered to indicate statistical significance.

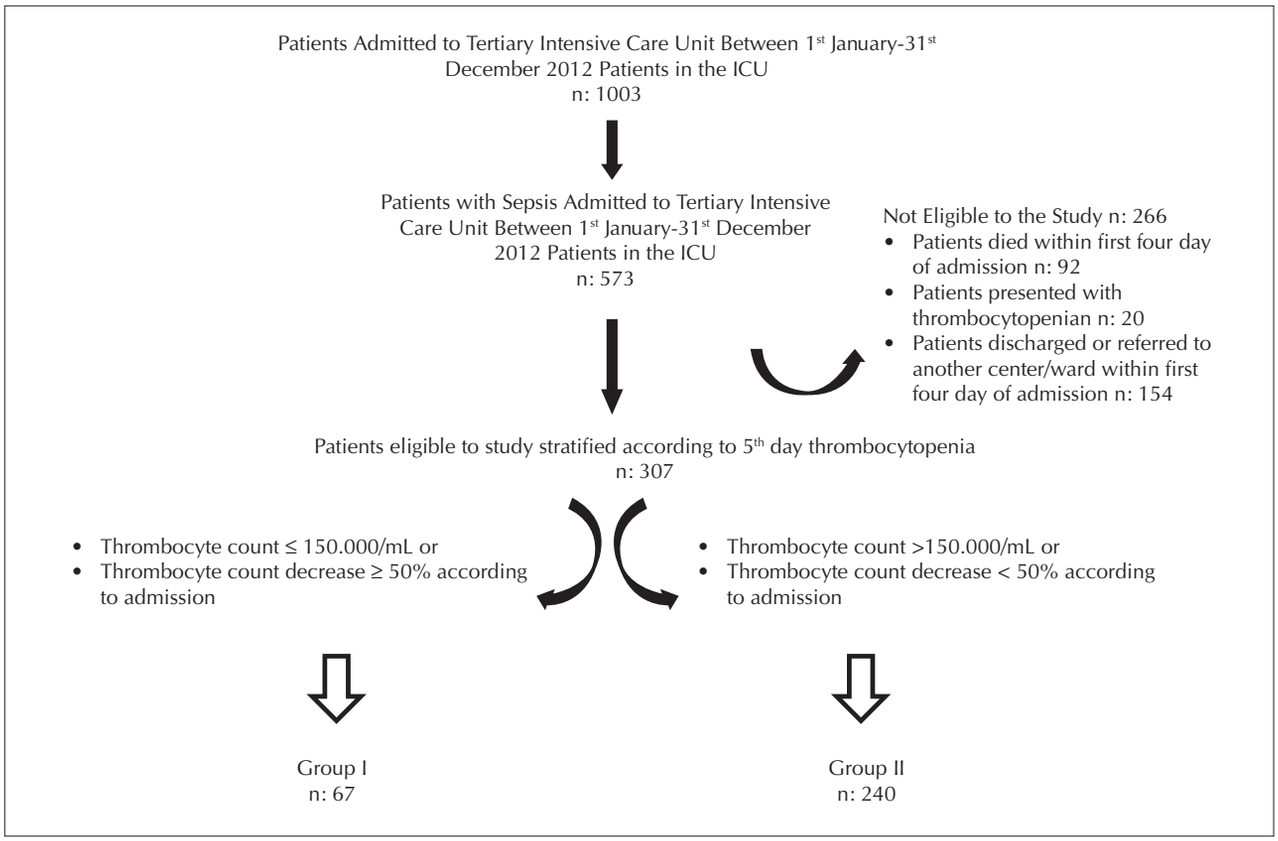

Figure 1. CONSORT diagram showing patient enrolment and stratification.

RESULTS

Patient enrolment and stratification are shown in the CONSORT diagram in Figure 1. Sepsis criteria were present in 573 (57.1%) of all 1003 patients admitted to the ICU during the study period. Septic shock was observed in 120 (39.1%) of the patients with sepsis.

Demographic characteristics, comorbidities, the performance of long-term oxygen therapy, and the performance of NIMV were compared between the two groups (Table 1). Most patients were male and > 65 years old. The characteristics of both groups were similar, except that the thrombocytopenic group had a significantly higher incidence of cancer as a comorbidity (p= 0.001). There were no significant differences in the number and frequency of SIRS signs between the two groups.

Laboratory values, APACHE II scores, and BMIs at admission as well as the patients' pre-ICU locations are shown in Table 2. Patients in Group 1 had significantly higher APACHE II scores and were more frequently transferred from other centers.

Microbiological samples were taken from 237 patients (77%). An agent was isolated in 92 (38.8%) of these patients. Gram-negative agents constituted most of the isolated pathogens. The most frequent were *Acinetobacter baumannii* (n= 40, 28.9%), *Pseudomonas aeruginosa* (n= 16, 11.6%), and *Klebsiella pneumoniae* (n= 15, 10.9%).

The application of mechanical ventilation, lengths of ICU and post-ICU hospital stay, and mortality rates of the two groups are shown in Table 3. The mortality, septic shock, and IMV rates were significantly higher in Group 1.

The application of mechanical ventilation and ICU outcomes are summarized in Figure 2. Group 1 patients who underwent direct IMV without NIV had a mortality rate of 73.3% (11 of 15 patients), which was significantly higher than that in Group 2 (p= 0.001).

Sex, APACHE II score at admission, serum albumin level, thrombocyte level on ICU days 1 and 5, presence of septic shock, serum CRP level, isolated pathogens, comorbidities, application of IMV and NIMV, and length of ICU stay were added to the logistic regression model to analyze the risk of mortality among patients with severe sepsis staying more than 4 days in the ICU. Thrombocytopenia on ICU day 5, the presence of septic shock, male sex, and a low albumin serum level were associated with an increased mortality rate of 80.1% in the regression model (Table 4).

A 12-month follow-up of 238 patients discharged from the ICU revealed that 124 (52.1%) of these patients had died. Half of the patients died within the first 2 months of discharge. Kaplan-Meier analysis revealed no statistically significant effects of thrombocytopenia on ICU day 5 (Figure 3).

DISCUSSION

This study showed that thrombocytopenia on the fifth day of ICU admission is a risk factor for ICU mortality, but not for long-term mortality, among patients with sepsis and acute

Table 1. Demographics, co-morbidities, presence of long-term oxygen therapy, and NIV

	Group 1 (n= 67)	Group 2 (n= 240)	p
Age, mean ± SD	68 ± 11	67 ± 13	0.67
Female %	26.8	24.5	0.71
APACHE II score, mean ± SD	25 ± 7	22 ± 7	0.003
Body mass index, kg/m^2, median (IQR)	25 (20-29)	23 (20-28)	0.35
C-reactive protein, mg/L, median (IQR)	97.3 (37.8-134.0)	79.1 (31.8-144.0)	0.79
Comorbidities, n (%)			
COPD	30 (44.8)	136 (56.7)	0.08
Diabetes mellitus	17 (25.4)	48 (20.0)	0.34
Hypertension	25 (37.3)	69 (28.8)	0.18
CAD	4 (6.0)	31 (12.9)	0.11
CRF	4 (6.0)	9 (3.8)	0.43
CVA	1 (1.5)	12 (5.0)	0.21
Malignancy	20 (29.9)	27 (11.2)	0.001
Respiratory support before ICU, n (%)			
Long-term oxygen therapy	28 (43.1)	118 (50.0)	0.32
Home NIMV	12 (18.5)	53 (22.6)	0.48

SD: standard deviation; APACHE: acute physiology and chronic health evaluation; IQR: interquartile ratio; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CRF: chronic renal failure; CVA: cerebrovascular accident; NIMV: non-invasive mechanical ventilation.

Table 2. Pre-ICU length of stay/location and laboratory data of the two groups at ICU admission

	Group 1 (n= 67)	Group 2 (n= 240)	p
Pre-ICU length of hospital, days, median (IQR)	5 (1-10)	4 (1-8)	0.99
Pre-ICU location, n (%)			
Medical ward	34 (50.7)	108 (45.0)	0.037
Surgical ward	1 (1.5)	9 (3.8)	
Outer center	17 (25.4)	34 (14.2)	
Emergency	15 (22.5)	89 (37.1)	
Hemogram values			
Leucocyte, 10^3/µL, mean ± SD	13.6 ± 7.3	14.5 ± 6.8	0.35
Hemoglobin, g/dL, mean ± SD	11.5 ± 2.6	11.8 ± 2.2	0.33
Thrombocyte, 10^3/µL, median (IQR)	165 (122-267)	273 (220-349)	0.001
Biochemistry values			
Glucose, mg/dL, median (IQR)	142 (115-195)	149 (119-191)	0.45
Blood urea nitrogen, mg/dL, mean ± SD	38 ± 21	28 ± 16	0.001
Creatinine, mg/dL, median (IQR)	1.13 (0.78-1.56)	0.79 (0.65-1.09)	0.001
SGOT, U/L, median (IQR)	28 (19-65)	24 (18-39)	0.067
SGPT, U/L, median (IQR)	27 (16-49)	23 (14-43)	0.27
Sodium, mmol/L, mean ± SD	137 ± 8	138 ± 6	0.87
Potassium, mmol/L, mean ± SD	4.5 ± 0.8	4.5 ± 0.7	0.77
INR, mean ± SD	1.35 ± 0.48	1.26 ± 0.50	0.19
Arterial blood gas analysis			
pH, mean ± SD	7.31 ± 0.13	7.33.13	0.29
$PaCO_2$, mmHg, mean ± SD	63.0 ± 29.2	65.7 ± 26.2	0.47
PaO_2/FiO_2, median (IQR)	155 (106-229)	160 (123-216)	0.58
HCO_3, mmol/L, mean ± SD	29.0 ± 9.2	33.5 ± 24.5	0.14

ICU: intensive care unit; IQR: interquartile ratio; SD: standard deviation; CRP: C-reactive protein; µL: microliter; mg/dL: milligram/deciliter; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamate pyruvate transaminase; U/L: units/liter; mmol/L: millimoles per liter; INR: international normalized ratio; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; mmHg: millimeter of mercury; PaO_2: partial pressure of oxygen in arterial blood; PaO_2/FIO_2: pressure of arterial oxygen to fractional inspired oxygen concentration; HCO_3: bicarbonate.

respiratory failure. Additional risk factors for ICU mortality were male gender, the presence of septic shock, and a low serum albumin level.

The mechanism of thrombocytopenia in sepsis is not completely clear. Hemophagocytosis may occur, consisting of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, hypothetically due to stimulation with high levels of macrophage colony-stimulating factor (M-CSF) in sepsis. Platelet consumption may also play an important role in patients with sepsis because of the ongoing generation of thrombin (which is the most potent activator of platelets *in vivo*) [18].

Studies of patients with sepsis hospitalized in the ICU have reported an overall mortality of 20%-30% [19,20]. Sepsis combined with septic shock is known to increase mortality. Many studies have shown that mortality associated with shock ranges from 20%-70%. This wide range varies according to factors such as underlying diseases, sex, and the presence of acute respiratory distress syndrome (ARDS) [19-21]. Therefore, the Surviving Sepsis Campaign aims to prevent the development of sepsis and shock and to treat shock as soon as possible once it develops. The overall mortality rate in patients with sepsis in our study was 42.5%, while the mortality rate in patients with septic shock was 22.3%. These rates are consistent with those reported worldwide [21,22]. In total, 51.7% of patients had sepsis criteria among those hospitalized in the ICU during the study period. Meanwhile, septic shock was observed in 23.1% of these patients during application of the sepsis protocol. The overall incidence of septic shock in our patients was 11.9%, which is compatible with data reported worldwide. Previous

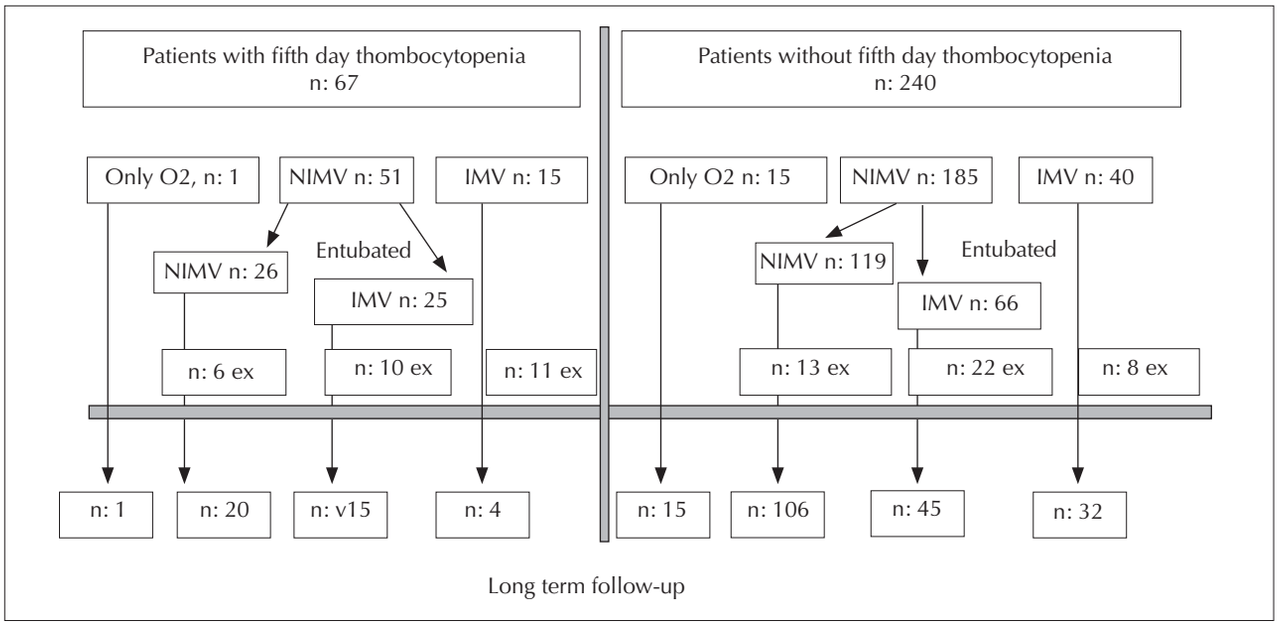

Figure 2. Mechanical ventilation in severe sepsis patients with/without fifth day thrombocytopenia.
NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation.

Table 3. ICU mortality rate, application of mechanical ventilation, length of stay at ICU and hospital after ICU of the two groups

	Group 1 (n= 67)	Group 2 (n= 240)	p
MV support, n (%)	66 (98.5)	225 (93.8)	0.12
NIMV, n (%)	51 (76.1)	185 (77.1)	0.87
NIMV, day, median (IQR)	6 (2-10)	5 (3-7)	0.46
IMV, n (%)	40 (59.7)	106 (44.2)	0.024
IMV, day, median (IQR)	6 (3-8)	5 (2-8)	0.27
Presence of septic shock, n (%)	36 (53.7)	84 (35.0)	0.005
ICU length of stay, day, median (IQR)	9 (7-12)	8 (6-11)	0.067
ICU mortality, n (%)	27 (40.3)	42 (17.5)	0.001
Post-ICU length of hospital stay, day, median (IQR)	7 (4-10)	8 (5-12)	0.53

MV: mechanical ventilation; NIMV: noninvasive mechanical ventilation; IQR: interquartile ratio; IMV: invasive mechanical ventilation; ICU: intensive care unit.

Table 4. Mortality risk factors for patients with severe sepsis after logistic regression analysis

	Odds ratio	95% confidence interval	p
Fifth day thrombocytopenia at ICU	3.03	1.15-7.45	0.025
Presence of septic shock	4.97	1.79-13.86	0.002
Male gender	3.61	1.27-10.23	0.001
Low albumin level at ICU admission	0.19	0.07-0.52	0.001

ICU: intensive care unit.

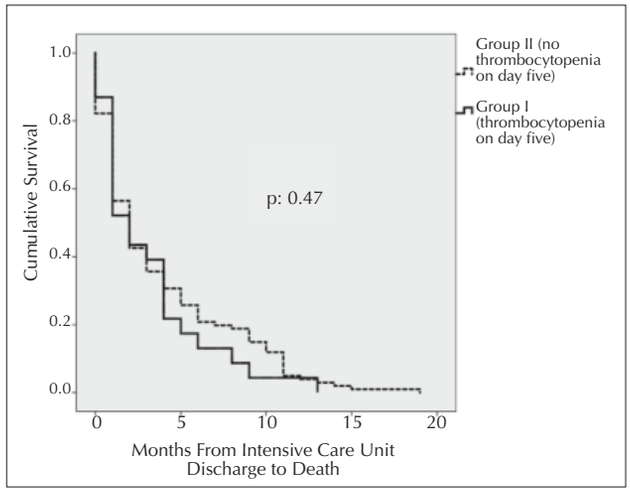

Figure 3. Long-term survival analysis of groups using Kaplan-Meier analysis after ICU discharge.

studies have reported that patients with septic shock are usually > 65 years old, male, and have comorbidities that suppress the immune system, particularly cancer [21,23]. Septic shock and male gender increased the risk of mortality 4.9- and 3.6-fold, respectively, in the present study. Because the average age of the patients in our study was 67 years, we could not demonstrate that age > 65 years is a risk factor for mortality.

Thrombocytopenia is a sepsis marker in patients with hematologic organ dysfunction [2]. It is also a significant predictor of mortality in patients with blood infections, pneumonia, and ARDS [24,25]. In a similar study performed 22 years ago with a smaller sample size than ours, a 58% incidence of thrombocytopenia and a 51% mortality rate were found among patients with sepsis [26]. Using the current sepsis protocol, we found a 40% mortality rate in the present study. In a systematic review of 6894 patients in

different ICUs (internal medicine, surgical, mixed, and trauma), the incidence of thrombocytopenia at ICU admission ranged from 8.3% to 67.6% [27]. Additionally, thrombocytopenia persisted in 13%-44% of patients during their ICU stay and was a risk factor for mortality in six of eight studies included in the review. The incidence of thrombocytopenia was 21.8% on the fifth day of the ICU stay in our study population. These variations can be explained by the differences in the definitions of thrombocytopenia; we used a definition of < 150.000/μL in the present study. Other studies have used cut-off values of 30.000, 50.000, and 100.000/μL. Worsening of thrombocytopenia during the ICU stay, particularly from day 4 to 7 of the ICU stay, has been reported as a risk factor for mortality in previous studies [6,27]. The mortality rate was two times higher in patients with severe sepsis and thrombocytopenia on the fifth day of the ICU stay in our study. Additionally, septic shock developed in half of the patients with thrombocytopenia and in one-third of the patients without thrombocytopenia. Various mediators involved in the pathogenesis of sepsis and endothelial permeability are also likely to be effective in the production of platelets and their function. Further study of platelet function and production may lead to new approaches in the treatment of septic shock.

Although few data are available on the long-term post-ICU mortality of patients with sepsis, a retrospective study showed that the life expectancy of patients who were admitted to the ICU with septic shock and survived for at least 30 days after discharge decreased from 8 to 4 years [28]. In our study, after a 12-month follow-up of patients with sepsis, male patients with septic shock were found to have shorter survival times; however, the difference was not statistically significant. Two articles published in 2004 and 2009 reported mortality rates of 36% and 37%, respectively, after prospective follow-up of patients with sepsis for 12 months; these rates were lower than the mortality rate in the present study (52.1%) [29,30]. Additionally, half of our patients died within the first 2 months of ICU discharge. This can be explained by the fact that nearly half of our patients were admitted with a diagnosis of end-stage chronic obstructive pulmonary disease (COPD).

In the present study, 61.3% of patients had positive culture results, and the rate of culture positivity was identical in the thrombocytopenic and non-thrombocytopenic groups. The most frequently isolated agents were *A. baumannii* (28.9%), *P. aeruginosa* (11.6%), *K. pneumoniae* (10.8%), and *Staphylococcus aureus* (5.1%). In an international multicentre study that examined 13.796 patients, culture specimens were taken from 51% of patients, and 70% of these cultures were positive [31]. In this same multicentre study, Gram-negative agents were mostly isolated in 62% of cases [31]. The high rate of culture isolation of *A. baumannii* in our patients may have been associated with their pre-ICU location and clinical features. Most patients were admitted to the ICU from the ICU of another center or ward. Additionally, these patients had a history of broad-spectrum antibiotic use as well as frequent and prolonged hospital admissions, which increases susceptibility to resistant pathogen growth. The higher rate of isolation of resistant pathogens in the thrombocytopenic group suggests that throbocytopenia is induced by uncontrolled infection due to these pathogens.

In this study, NIV and IMV were applied in approximately 95% of patients, while 47.6% were followed up with IMV. However, IMV was applied two-thirds more frequently in patients with thrombocytopenia on day 5 of the ICU stay. NIV was applied at a similar rate in both groups of patients. The mortality rate of patients with thrombocytopenia on day 5 was higher among those patients who underwent IMV directly upon admission than in those who underwent IMV after NIV failure (73.3% vs. 40.0%, respectively). The mortality rate in patients who underwent only NIV treatment was lower. Thus, the presence of thrombocytopenia adversely and significantly affects the response to applied mechanical ventilation and to the mortality rate. Application of NIV to clinically unstable patients with shock and ARDS is controversial and has a low success rate [32]. Because most of our patients were diagnosed with COPD, NIV might be regarded as the first-line mechanical ventilation application unless a specific contraindication exists. Additionally, because most of our patients had COPD, intubation may have been performed in worse clinical conditions, explaining the poorer prognosis.

There were several limitations to our study. First, this was a retrospective, single-center study. However, the follow-up and treatment of patients and the data collection were performed by the same physician group using the same optimized computer-based program; thus, our study provides significant international data. Second, the study was conducted in a respiratory ICU and included only patients with severe sepsis and respiratory disease. The results may differ in a different population; however, it should be noted that sepsis with a pulmonary origin constitutes the clinical condition in half of the patients in general ICUs. Third, we did not perform microbiological examinations in half of our patients. In our respiratory ICU, we routinely perform endotracheal aspiration to obtain culture specimens from intubated patients. However, sputum expectoration is not always possible in patients who are not intubated, and contamination from the oropharynx is also a problem in these patients. Finally, we could not exclude patients with possible HIT because we could not detect antibodies directed against the PF4/heparin complex in our laboratory. However, the incidence of HIT is low in ICU patients. In a large prospective study comprising 5.949 ICU patients (2.751 after cardiac surgery and 3.198 after thoracic surgery), HIT was clinically suspected in 1.7% at a median of 5 (range, 4-9) days after ICU admission [33]. Most of the studies investigating thrombocytopenia and ICU mortality exclude HIT patients using the presence of clinical criteria suggestive of HIT and the presence of platelet factor-4 antibodies [34,35]. On the other hand, in patients with HIT, the platelet count usually falls 5-14 days after heparin is first administered, and we divided our patients in two groups according to the platelet count on the fifth day because of the absence of the immunologic test. By this method, we likely eliminated patients with heparin-induced thrombocytopenia.

As far as we know, this is the first retrospective study in which patients were classified according to the fifth day thrombocyte count.

This study also had several strengths. It is one of only a few comprehensive studies investigating the long- and short-term outcomes of patients with thrombocytopenia and sepsis in the ICU. Using a current sepsis protocol, the impact of thrombocytopenia on the prognosis of sepsis was investigated in broad and specific patient populations. Patients were treated by the same intensivists and pulmonary specialists working in the ICU with 7/24 shifts, thus minimizing implementation differences.

In conclusion, this study found that thrombocytopenia on the fifth day of the ICU stay increases ICU mortality threefold. The need for IMV and frequency of septic shock were greater in these thrombocytopenic patients admitted to our ICU. We showed that male sex, a low blood albumin level, and the presence of septic shock and thrombocytopenia on day 5 of the ICU stay increased the risk of mortality to 80%. Application of IMV upon admission to the ICU significantly increases mortality. The measurement of thrombocytopenia in the ICU, which is easy and low-cost, may help to predict mortality. Thus, precautions can be taken early in patient treatment and follow-up. As we know, early intervention is crucial in the approach to sepsis.

Ethics Committee Approval: Ethic committee approval of this study was received from Internal Review Board of Kartal Lütfi Kırdar Teaching Hospital.

Informed Consent: Because of retrospective nature of study consent form was not taken from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.K., B.B., C.S., E.A.Ö., H.B.T.; Design - B.B., C.S., Z.K., H.B.T., F.K., G.H., A.Y., G.G., Ö.M.; Supervision - Z.K., B.B., A.Y., H.B.T.; Resources - B.B., F.K., G.H., E.A.Ö., Z.K., C.S., Ö.M., N.A.; Materials - B.B., E.A.Ö., H.B.T., G.H., A.Y., N.A., G.G.; Data Collection and/or Processing - C.S., B.B., E.A.Ö., N.A., Ö.M., H.B.T.; Analysis and/or Interpretation - Z.K., C.S., B.B., N.A., G.G., Ö.M., H.B.T.; Literature Search - B.B., C.S., Z.K., E.A.Ö., G.H., A.Y., F.K.; Writing Manuscript - B.B., C.S., Z.K., G.G., Ö.M., N.A., F.K.; Critical Review - B.B., Z.K., G.G., N.A., Ö.M., F.K.; Other - B.B., G.G., F.K., N.A., H.B.T.

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ORIGINAL INVESTIGATION

Can a Computer-Based Prescription of Free Medication Increase Smoking Cessation Rates Efficiently?

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Abstract

OBJECTIVES: In 2011, in the context of a research project, bupropion and varenicline were distributed to smoking cessation clinics by the Ministry of Health of Turkey to be prescribed free of charge by a computer-based system. In the present study, we compared smoking cessation rates between patients who were prescribed free medications during the period of the project and those who had to pay for their medication.

MATERIAL AND METHODS: Six hundred four patients who applied during the project period were given either bupropion or varenicline, which were prescribed using an algorithm-based computer system. Three hundred sixteen patients who applied after that period were prescribed medicines deemed appropriate by the attending physician but had to pay for the medication on their own. Follow-up visits were arranged for one year. Carbon monoxide (CO) levels in the expired air were used as indicators of cessation.

RESULTS: A total of 537 patients began treatment, of which 438 (81.6%) applied during the first period (group 1) and 99 (18.4%) applied during the second period (group 2). The mean age and concomitant disease presence were higher in the second-period patients ($p< 0.05$). Advanced age, comorbidities, pathological findings in spirometry, and chest X-ray were also higher in those who paid for the cost of their treatment ($p= 0.009$, 0.001, 0.006, 0.001, respectively). Smoking cessation rates were found to be 14.8% and 27.3% after six months ($p= 0.008$) and 10.7% and 18.2% after one year ($p= 0.059$), respectively, for group 1 and group 2. Age, dependence score, cigarettes smoked (as pack-years), and percentage of patients who paid for the treatment were found to be significantly higher ($p< 0.001$, 0.021, 0.018, 0.001, respectively) for those who quit smoking at the end of six months. For the patients who quit smoking at the end of one year, age was found to be significantly higher ($p= 0.008$), and the number of males was higher, although the difference was not statistically significant ($p= 0.05$). When logistic regression analysis was applied, age, dependence score, and paid treatment were found to be independent variables ($p= 0.002$, 0.008, 0.012, respectively) for those who quit smoking at the end of six months. Only age was found to be an independent variable for those who quit smoking at the end of one year ($p= 0.029$).

CONCLUSION: More smokers could receive treatment by the distribution of free drugs. However, quitting rates at the end of six months were higher when patients had to pay for their treatment. On the other hand, quitting rates at the end of one year were not affected by whether the treatment was paid for or free of charge. The most important factor increasing quitting rates at the end of six months and one year was found to be advanced age.

KEY WORDS: Smoking cessation, smoking cessation policies, treatment efficiency

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INTRODUCTION

Tobacco dependence is a chronic and recurrent disorder that is the foremost preventable cause of death worldwide. In the whole world, 70% of all smokers want to completely quit smoking. Each year, 40% of them try to quit, but only 3-5% can successfully sustain cessation for a long term on their own [1,2]. However, success rates of 15% to 30% can be achieved by administering treatments recommended by guidelines [3,4]. The most effective method for smoking cessation is a multidisciplinary approach encompassing psychological, behavioral, and pharmacological therapies [1-6].

This study was presented as an oral presentation at the TÜSAD 35th Annual Congress on October 3-6, 2013, Çeşme, Turkey.

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Nicotine replacement therapy (NRT), bupropion, and varenicline combined with behavioral therapies are the first-line pharmacological treatments recommended in smoking cessation centers [3-7]. In clinical trials, long-term cessation rates in smokers with smoking-related disorders were reported to be 15-29%, 27-29%, and 43-48% for nicotine therapy, bupropion, and varenicline, respectively [5]. In addition to pharmacological treatments, intensive face-to-face or group interviews providing psychological support and phone call follow-ups increase smoking cessation rates [3-6].

Treating tobacco dependence is very important economically in that it can reduce the cost of treatment of chronic diseases and complications such as heart disease, pulmonary disease, cancer, and delayed wound healing. Without supportive systems and policies, individual clinicians may not be able to assess and treat tobacco dependence sufficiently. Just as clinicians must assume responsibility for the treatment of tobacco dependence, so also must health care administrators, insurers, and purchasers for crafting policies and providing resources that result in consistent and effective tobacco dependence treatment [3-5,8]. The updated guidelines [4] suggest that sufficient resources should be allocated for clinician reimbursement and systems support to ensure the delivery of efficacious tobacco use treatments.

A global adult tobacco survey conducted in 2008 showed that smoking rates in Turkey were 31.2% (47.9% in men and 15.2% in women) [9]. The Action Plan for National Tobacco Control Program was put into effect over the last five years in Turkey [10,11]. Smoking prohibition by law and increases in cigarette costs helped decrease smoking rates by 10.7% [9]. In this regard, cessation counseling and supportive interventions were paid by social security institutions as a component of this program [10,11]. However, the costs of pharmacological treatments are not yet included in the reimbursement programs of either Social Security Institution or private health insurance companies. In January 2011, according to a Council of Minister's decision, the Ministry of Health of Turkey purchased 350.000 boxes of bupropion and varenicline (150.000 of bupropion and 200.000 of varenicline) in the context of a research project. These medications were distributed to smoking cessation clinics to be prescribed free of charge by an online computer system [12].
With this study, we aimed to assess the effects of a computer-based free-of-charge provision of smoking cessation medications on smoking cessation rates.

MATERIALS AND METHODS

The study was planned according to the World Medical Association Declaration of Helsinki (2008). It is a retrospective cohort study.

Nine hundred twenty patients who applied to our smoking cessation clinic between April 2011 and June 2012 were included in this study. Six hundred four of these patients applied during the prescription of free pharmacological treatments between April 2011 and December 2011 (first nine-month period), while 316 applied between January 2012 and June 2012 (second six-month period) when they had to meet the cost of this treatment on their own.

On first interview, all patients were asked about their comorbidities and tobacco use statuses. The Fagerstrom test for Nicotine Dependence was used to assess their dependence scores [13]. Physical examinations and pulmonary function tests were performed (Sensor Medics Vmax22, CareFusion, San Diego, California,USA). The carbon monoxide (CO) level in expired air was measured (piCO Smokerlyzer, Bedfont Scientific Ltd, Harrietsham Maidstone Kent, England), and chest X-rays were taken. Interviews with patients, the interpretation of pulmonary function tests, and the measurement of CO levels in expired air were conducted by the same physician.

For group 1, comorbidities and tobacco use statuses of all patients were entered in to the hospital patient registration system and also to an online patient registration system regulated by the Ministry of Health. In total, 350.000 boxes of varenicline and bupropion were purchased on the context of the project by the Ministry of Health, and these were provided to smoking cessation clinics, including ours. These medications could be prescribed for a patient only when the aforementioned computer system deemed it appropriate. This computer system decided whether to prescribe varenicline or bupropion taking into account the patient's age, gender, smoking status, Fagerstrom score, comorbidities, and contraindications to either medication [12]. The system had no rules for selection of any of the two drugs in the case of absence of any absolute contraindication for bupropion. Smokers with a history of depression received none of them, and in those cases, the attending physician prescribed NRT. The provision was only free of charge if the patients were prescribed medications decided by the computer system. NRT was not included in the project, and if prescribed by the attending physician the cost had to be paid for by the patient.

The information on the group 2 patients was only entered in to the hospital patient registration system. This group was prescribed medications deemed appropriate by the attending physician after a face-to-face interview and they paid the cost on their own because the free medication provision period was over and the costs of the smoking cessation medications were not included in the reimbursement programs. The physician prescribed bupropion, varenicline, or NRT after taking all the medical characteristics into consideration, informing the patient about the drug side-effects, and asking for the patient's oral or transdermal drug choice. All patients were given an appointment to attend an interactive seminar in which epidemiology and the harmful effects of smoking; tobacco dependence, and the treatment options for cessation and the benefits of smoking cessation were discussed with the aid of visual slides. The seminars lasted 45 min and were performed twice weekly for groups of 8 to 10. After attending the seminar, group 1 patients were given the medications assigned by the computer system free of charge after their

informed consents were taken. Group 2 patients were given their prescriptions by the attending physician and they had to buy those medications from pharmacies. One hundred sixty-seven patients who could not receive any drugs by the system and 217 patients who learned that they could not receive free drugs in the second period refused to buy the medication or start the pharmacological therapy. All those who started the treatment in the first period were assigned to group 1, and those who started treatment in the second period were assigned to group 2. All patients were given control appointments once a month for the first three months, then once every two months for the following four months, and once every three months for the rest of the one year follow-up period. During the control visits, the patients were questioned about their smoking status and medication side-effects. CO levels in the expired air were measured. Patients with a CO level between 0 and 5 parts per million (ppm) were accepted as non-smokers, while those with ≥ 6 ppm were considered still to be smokers [14,15]. Patients who did not attend the control visits were considered as non-quitters. The data were entered into the hospital registration system. Analyses were performed after all patients were followed-up for one year.

Statistical Analysis

Data from the standardized medical reports were transferred to the Statistical Package for the Social Sciences (SPSS Inc, 17.0, Chicago Illinois, USA) program by the lead researcher. The data were analyzed for the frequency distributions. Comparisons were made for each period and for each group of patients who had therapy. The chi-square test was used in the analysis of the categorical variables. The Kolmogorov–Smirnov test was used to test normality of the numerical variables. For normally distributed variables, an independent samples t-test was performed. Logistic regression analysis was used for the confounding factors. The statistical significance level was taken as a p value < 0.05.

RESULTS

Between April 2011 and June 2012, a total of 920 patients applied to the smoking cessation clinic. The average age of all patients was 42.9 ± 11.5, of which 548 (59.6%) were males and 372 (40.4%) were females. The average amount of smoking was 28.2 ± 18.8 pack-years (mean package of cigarettes smoked per day times years of smoking), the mean Fagerstrom Nicotine Dependence Test score was 6.1 ± 2.3, and the average CO level in the expired air was 14.2 ± 8.5 ppm. For 32.8% of the patients, pathological findings consistent with small airway obstruction in 13.2%, obstructive disease in 18%, and restrictive disease in 3.4% were found in pulmonary function tests. In chest X-rays, 52.5% of the patients had pathological findings (increased aeration, increased bronchovascular markings, milimetric nodules, opacity, etc.). In 259 (28.2%) patients, comorbid diseases (COPD, asthma, cardiovascular disease, cancer, depression, cerebrovascular disease, diabetes, etc.) were present.

Out of all patients, 604 (65.7%) applied during the prescription of free pharmacological treatments by the online system (first period), and 316 (34.3%) applied when they were prescribed medication by the attending physician and had to meet the cost of this treatment on their own (second period). Mean age (42.3 years vs 44.0; p= 0.033), mean CO level in the expired air (13.4 ppm vs 15.3; p= 0.001), and the presence of concomitant disease (22.8% vs 38.6%; p= 0.001) were higher in the second period patients.

A total of 537 patients began treatment, of whom 438 (81.6%) applied during the first period (group 1), and 99

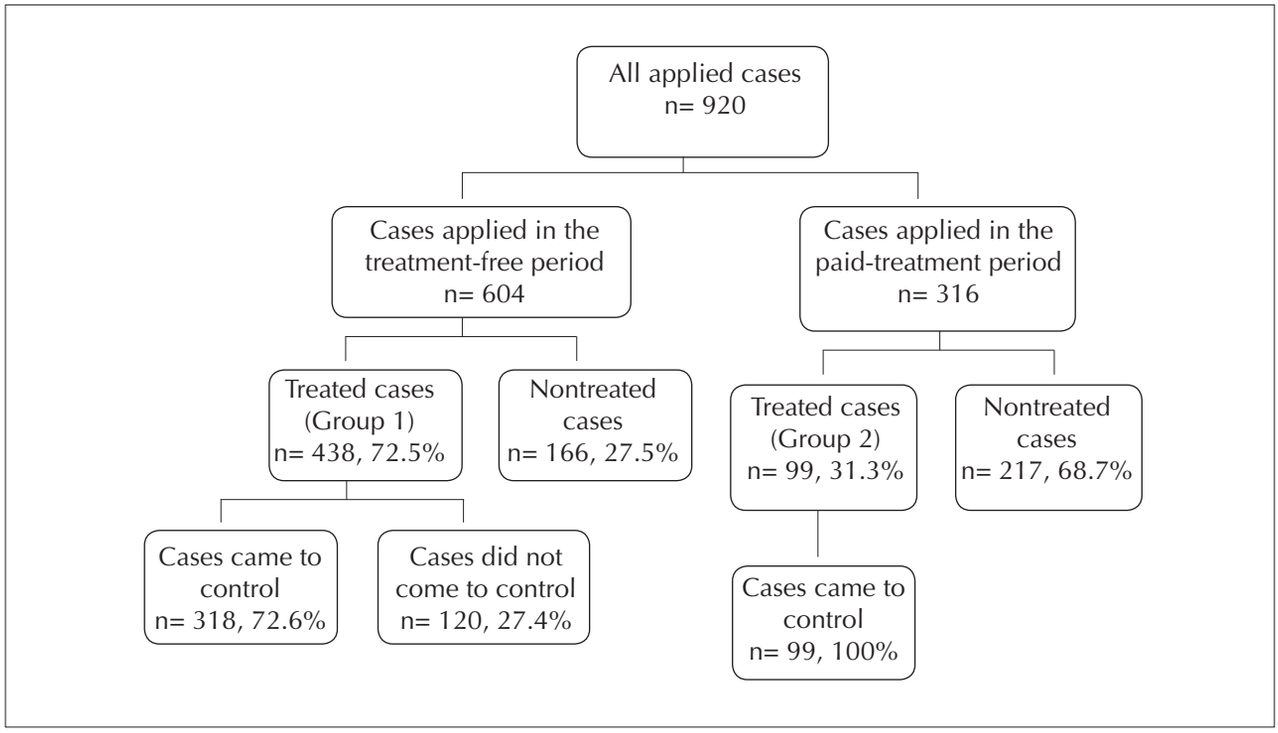

Figure 1. Distribution of smokers.

(18.4%) during the second period (group 2). Of all the treated patients, 417 (77.6%) attended control visits at least once. Three hundred eighteen (72.6%) of the group 1 patients and all group 2 patients attended the first control visit (Figure 1).

Of group 1 patients, 297 (67.9%) used varenicline, 140 (31.9%) used bupropion, and 1 (0.2%) used nicotine patches plus bupropion. Of group 2 patients, 32 (32.3%) used varenicline, 32 (32.3%) used bupropion, 28 (28.2%) used nicotine patches, 3 (3.1%) used nicotine patches plus bupropion, and 4 (4.1%) used nicotine patches plus nicotine gum. Considering the medications, the success rates after one year in the two groups were 13% and 12.5% for varenicline, 5.8% and 22.8% for bupropion, respectively, and 14.7% for NRT in the second period.

When the characteristics of the patients treated in the two groups were compared, in group 1, the patients were younger (43.0 ± 10.8 vs. 46.8 ± 13.4, p= 0.009). The presence of concomitant disease (26% vs. 45.5%, p= 0.001), the incidence of pathological findings in pulmonary function test (PFT) (23.5% vs. 42.4%, p= 0.001), and the presence of pathological findings in chest X-rays (39.8% vs. 56.5%, p= 0.006) were also higher in group 2. More patients used varenicline (67.9% vs. 32.2%, p< 0.001), and no patients used nicotine patch (0% vs. 32.3%, p< 0.001) in group 1. There were no differences between the two groups in terms of gender, average duration of smoking, Fagerstrom score, and bupropion usage (p> 0.05) (Table 1).

During the control visits, a total of 60 patients (11.5%) reported drug side-effects (tachycardia in 0.2%, sleep problems in 1.5%, depression in 0.7%, blood pressure related problems in 0.3%, headache in 0.5%, nausea in 2.9%, vertigo in 1.9%, and allergic reactions in 1.5%). The incidence of side-effects were not different in the two groups (10.7% vs. 15.2%, p= 0.214) (Table 1).

Smoking cessation rates for one month (43.5% vs. 75.8%, p< 0.001), for three months (25.4% vs. 42.4%, p= 0.002), and for six months (14.8% vs. 27.3%, p= 0.008) were higher in group 2. There was no difference statistically between the two groups after one year (10.7% vs. 18.2%, p= 0.059) (Table 2).

When the characteristics of six-month and one-year quitters/non-quitters were compared, age was greater for patients who quit at the end of six months and one year (p< 0.001, p= 0.003, respectively). The percentage of men was higher for those who quit smoking at one year. The difference was close enough to be statistically significant (p= 0.050). For those who quit at six months, the Fagerstrom score, cigarettes smoked (as pack-years), presence of pathological findings in chest X-rays, and the percentage of patients who paid were found to be significantly higher (p= 0.021, 0.018, 0.013, 0.012, respectively) (Table 3).

When logistic regression analyses were made, advanced age, higher Fagerstrom score, and paying for the cost of the treatment were found to be independent variables (p= 0.002, 0.008, 0.037, respectively) for those who quit smoking at six months. Only age was found to be an independent variable for those who quit smoking at the end of one year (p= 0.029).

DISCUSSION

The high smoking rates (31.2%) [9] in Turkey raise the need for free quitting drugs in national tobacco control programs. The current study compares the cessation success rates in a period when patients could receive free drugs distributed by the Ministry of Health and a second period when patients

Table 1. Characteristics of the treated patients

	All patients n= 537	Group 1 (free) patients n= 438	Group 2 (paid) patients n= 99	p
Mean age (years)	43.7±11.4	43.0±10.8	46.8 ± 13.4	**0.009**
Gender				
Male, %	56.6	55.4	61.6	0.322
Female, %	43.4	44.6	38.4	
Mean Fagerstrom score	6.2 ± 2.3	6.1 ± 2.3	6.3 ± 2.4	0.533
Mean smoking duration (pack-years)	28.0 ± 17.7	27.4 ± 17.6	30.9 ± 17.8	0.097
Concomitant disease, %	29.6	26	45.5	**0.001**
Pathological findings in chest X-ray, %	42.8	39.8	56.5	**0.006**
Pathological findings in PFT, %	27	23.5	42.4	**0.001**
Bupropion, %	32.2	32.1	32.3	0.487
Varenicline, %	61.3	67.9	32.3	**< 0.001**
NRT, %	32	0	32.3	**< 0.001**
NRT+Bupropion, %	4	0.2	3.1	**< 0.009**
Medicine side-effects, %	11.5	10.7	15.2	0.214

NRT: nicotine replacement therapy; PFT: pulmonary function test.

Table 2. Smoking cessation rates observed in treated patients

	All patients n= 537	Group 1 (free) patients n= 438	Group 2 (paid) patients n= 99	p
For one month, n (%)	287 (53.5)	190 (43.5)	75 (75.8)	**< 0.001**
For three months, n (%)	153 (28.4)	111 (25.4)	42 (42.4)	**0.002**
For six months, n (%)	92 (17.8)	65 (14.8)	27 (27.3)	**0.008**
For one year, n (%)	65 (12.2)	47 (10.7)	18 (18.2)	0.059

Table 3. Characteristics of the patients who had quit/had not quit smoking after six months and after one year

	Quitters 6 months 1 year		Non-quitters 6 months 1 year		p	
	n= 90	n= 61	n= 447	n= 476	6 months 1 year	
Mean age (years)	48.9 ± 11.4	47.8 ± 11.1	42.6 ± 11.1	43.2 ± 11.4	**< 0.001**	**0.003**
Gender						
Male, %	67.7	68.8	55	55.6	0.079	**0.050**
Female, %	32.3	31.2	45	44.4		
Fagerstrom score	5.5 ± 2.5	5.8 ± 2.2	6.3 ± 2.3	6.2 ± 2.3	**0.021**	0.334
Smoking pack-years	32.3 ± 17.8	31.3 ± 15.1	27.2 ± 17.6	27.6 ± 18.0	**0.018**	0.166
Comorbidities, %	36.6	31.1	28.6	29.8	0.129	0.833
Pathological findings in PFT, %	39	38.1	31.3	31.8	0.173	0.351
Pathological findings in chest X-ray, %	64.2	55.3	49.3	51.6	**0.013**	0.606
Cases who paid for the cost on their own %	27.7	24.5	16.5	17.6	**0.012**	0.188
Bupropion, %	32.2	26.2	32.4	33.1	0.968	0.274
Varenicline, %	62.2	68.8	60.6	59.8	0.777	0.176
NRT, %	8	8.1	6	6.3	0.318	0.573

NRT: nicotine replacement therapy; PFT: pulmonary function test.

had to pay for the drugs themselves. This study is the only study on this subject and is of great importance for predicting economic policies on tobacco control in Turkey.

To summarize our findings, more patients could access smoking cessation therapies when treatment costs were covered by the government (438 of 604 patients during the first period vs 99 of 316 patients during the second period); however, contrary to what was expected, the cessation rates were not found to be higher in the group 1. One-, three, and six-month success rates were statistically higher for patients who paid for their own drugs. One-year success rates were higher but not statistically different in the group 2. Independent variables that affect six month quitting rates were advanced age, higher dependence score, and the patient paying the cost of treatment. The sole factor that affects quitting rates at one year was found to be advanced age. The mode of payment (paid vs. free of charge) and drugs used were not found to affect quitting rates at one year.

Considering the fact that there are few drug alternatives, the idea of the prescribing smoking cessation medications by a computer that would run on an algorithm taking into account medication contraindications and patient comorbidities might sound intriguing. Taking into account the large number of smokers, it would require a substantial amount of manpower to be able to treat all smokers efficiently. The provision of smoking cessation medications free of charge would also greatly increase applications to smoking cessation clinics, as was shown in our study too.

The American Public Health Association on Tobacco Control consensus reports prepared in 2000 [3] and 2008 [4] indicated that when tobacco dependence treatments were covered by social security institutions and private health insurance companies, the success rates of smoking cessation increased. Over time, the widespread implementation of this approach provides a 2–3.5% decrease in the prevalence of smoking [16]. It was also shown that the support of employers, environmental incentives, and pursued politics are also important factors to reach more smokers [17,18].

Although the provision of free services to all smokers may be attractive, it is possible that they attract less motivated smokers than services for which co-payments are required, thus diluting their effectiveness. In the study by Curry et al. [19],

although they showed that the rates of smoking cessation were lower in patients for whom treatment costs were completely met by employers, more patients could quit smoking because more smokers were able to access free treatment. Similarly, in our study, more patients could be treated in the free period and more patients could quit smoking, but smoking cessation rates after one year were found to be very low, in fact lower than that in the second period (10.5% vs. 18.2%).

With smoking cessation treatments, only a small portion of smokers can sustain long-term abstinence; however, they prevent many smoking-related diseases. For such diseases, they are accepted as gold standard treatments in terms of cost effectiveness [20-23]. Moreover, more premature births can be prevented by the treatment of smoker pregnant women for cessation. Medicaid, which is a health insurance system in the USA, covers at least one type of treatment modality for smoking cessation in 37 states (In some states, only costs for smoking cessation for pregnant women are covered, while in others, all costs for every type of treatment for smoking cessation are covered for every patient) [24-27]. Because it was shown by studies that when tobacco dependence treatments were totally covered by insurance, success rates were much higher than when they were only partially covered and patients had to pay for a percentage of the treatment [28]. It was also found that cessation rates would dramatically decrease (especially for low-income populations) when patients had to pay even for a small percentage of the treatment; therefore, it was concluded that all costs should be covered by the insurance system [24-28].

In Turkey, over the last five years, only behavioral and supportive therapies have been covered by the insurance system, but not pharmacological therapies [11]. When our clinic was provided with the medications to be prescribed by the computer system, this project was already announced to the public [12]. Because of that, we think that those who applied to our clinic during the first period were less motivated than those who applied during the second period. While all those who began pharmacological therapy in the second period attended follow-up visits, only 72% of the patients who began pharmacological therapy in the first period attended follow-up visits. In the first period, patients who could not receive any free medications by the system neither bought the drugs nor attended the control visits. However, 31% of the patients in the group 2 paid for the drugs themselves, and all these patients attended follow-up visits. This can be explained by the fact that the patients in the latter group were more motivated. In addition, the higher percentage of advanced age, the presence of concomitant diseases, and the presence of respiratory problems in group 2 might indicate the higher decisiveness in this group.

In our study, contrary to the aforementioned studies, cessation rates for one, three, and six months were significantly higher in group 2 patients who had to pay for the treatment costs. Even if we conclude that those in group 2 were more determined, taking into account the presence of concomitant diseases in this group, the results are still surprising. We think that this discrepancy was caused by the attending physician being restrained by the computer system's decisions when prescribing medications for group 1 patients. All of the patients in group 1 were treated with bupropion or varenicline, even if the physician wanted to use NRT instead in some of the patients, because NRT was not free of charge these patients did not want to pay for it. More than two-thirds of patients who applied after the end of the project declined any treatment and/or follow-up visits when they learned that they would have to pay for their treatment. Only 31% of those patients could be treated. This finding again underscores the importance of the coverage of smoking cessation treatments by the insurance system.

The main limitations of this study are as follows: this is a single-center study; therefore, the results might not reflect the entire population. Due to the retrospective design of the study, some data loss could have occurred. Patients who had not attended follow-ups were considered as non-quitters. Patients in group 1 were younger, and this might have affected the success rates as well.

In conclusion, though more smokers could receive treatment, free drug distribution did not increase long-term smoking cessation rates as expected. We thought that the introduction of a computer-based system that restricts the physicians' decision making would reduce the success rate of treatments for smoking cessation in our clinic. The fact that the presence of advanced age and comorbidities were higher among those who paid for the drugs and the advanced age among one-year quitters implies that the aforementioned medications must be free, at least for this group of patients. On the other hand, many more people could reach medical care for smoking cessation, which shows that with an insurance system that would cover the treatment costs for smoking cessation, smoking-related diseases and deaths would be prevented for more people, which would also reduce the impact of smoking-related disease treatments on the economy. The fact that this project's success rates were lower than expected indicates that the method of the project should be questioned and the cost of the drugs should be covered by the insurance system after they are prescribed by the attending physician. More studies on wider case groups are needed to draw more convincing conclusions.

Ethics Committee Approval: Ethics committee approval was not received for this study because the procedure of this study has included routin practises of smoking cessation outpatient clinic.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.S.; Design - B.S., B.Ç.; Supervision - B.Ç.; Resources - B.S., E.T.P., N.K.; Materials - B.Ç.; Data Collection and/or Processing - A.F., B.S., S.S.C., G.A.G.; Analysis and/or Interpretation - B.S., A.F., S.S.C.; Literature Search - B.S., N.K., E.T.P., E.S.; Writing Manuscript - B.S., A.F., E.S.; Critical Review - B.Ç.; Other - G.A.G., E.S.

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ORIGINAL INVESTIGATION

The Role of Endobronchial Biopsy in the Diagnosis of Pulmonary Sarcoidosis

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Abstract

OBJECTIVES: This study aimed to investigate the additional diagnostic value of endobronchial biopsy (EBB) in the diagnosis of pulmonary sarcoidosis.

MATERIALS AND METHODS: This retrospective cross-sectional study included 59 patients with a preliminary diagnosis of sarcoidosis who were admitted to the Pulmonary Diseases Outpatient Clinic of a tertiary healthcare center between January 2005 and October 2012. The socio-demographic characteristics of the patients as well as clinical and radiological findings were recorded. All patients, irrespective of the presence of an endobronchial lesion (EBL), underwent fiberoptic bronchoscopy (FOB); two to four specimens were taken using EBB from the carina of the right middle lobe in the patients with EBL.

RESULTS: Of the patients, 39 (66.1%) had normal bronchoscopic findings, while 5 had EBL. Diagnosis was based on EBB in 11 patients (18.6%). Six patients (15.3%) with normal bronchial mucosae were pathologically diagnosed by EBB. There was no statistically significant relationship between the diagnostic ratio of EBB and disease stage, extrapulmonary involvement, FOB findings, elevated lymphocyte rate in bronchoalveolar lavage (≥ 13%), a CD4/CD8 ratio of ≥ 3.5, and serum angiotensin-converting enzyme (ACE) level ($p > 0.05$).

CONCLUSION: EBB not only offers the advantage of a high diagnostic ratio in patients with mucosal abnormalities but also contributes to pathological diagnosis in patients with normal mucosa. We recommend using EBB to support diagnosis with a low complication rate for patients undergoing FOB with a preliminary diagnosis of sarcoidosis in healthcare centers, where endobronchial ultrasound (EBUS) is unavailable.

KEYWORDS: Diagnosis of sarcoidosis, fiberoptic bronchoscopy, endobronchial biopsy

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology that primarily affects the lungs and lymphatic system. Diagnosis is based on a compatible clinical presentation and imaging, as well as the presence of non-caseating granulomas in biopsy specimens, by excluding other causes of granulomatous diseases [1,2]. Fiberoptic bronchoscopy (FOB), which involves the acquisition of tissue specimens to eliminate other diseases, is a relatively simple procedure with a lower complication rate than other surgical procedures and is the primary diagnostic tool for sarcoidosis patients [1]. A pathological diagnosis can be achieved with the help of transbronchial lung biopsy (TBLB) and/or transbronchial needle aspiration (TBNA) of mediastinal and hilar lymph nodes. In addition, a compatible clinical presentation, imaging with lymphocytic alveolitis, and an increased ratio of CD4/CD8 lymphocytes support pulmonary sarcoidosis diagnosis in patients without a histopathological confirmation.

Today, with the introduction of real-time endobronchial ultrasound-guided TBNA (EBUS-TBNA) and transesophageal endoscopic ultrasound-guided fine needle aspiration, a higher number of patients is diagnosed with sarcoidosis [3-5]. Currently, endobronchial ultrasound (EBUS) is extensively used for mediastinal sampling; however, conventional bronchoscopic techniques are still the first choice in the diagnostic algorithm of sarcoidosis cases in many centers [1].

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The diagnostic efficiency of TBLB is particularly affected by parenchymal involvement as evidenced by radiographic studies, and patient compliance is a must for this procedure. On the other hand, TBLB may lead to serious complications including bleeding and pneumothorax. The diagnostic value of endobronchial biopsy (EBB) is high in the presence of bronchial mucosal lesions, although EBB is recommended for patients without visible mucosal lesions [6,7].

In this study, we investigated the additional diagnostic value of EBB, which is a relatively simple diagnostic procedure with a low complication rate, during FOB in the diagnosis of pulmonary sarcoidosis.

MATERIALS AND METHODS

Study Population

This retrospective cross-sectional study included 59 patients with a preliminary diagnosis of sarcoidosis who were admitted to the Pulmonary Diseases Outpatient Clinic of a tertiary healthcare center between January 2005 and October 2012 (Figure 1). The study was approved by the Celal Bayar University Scientific Research Ethics Committee in Manisa (07.03.2011/0057), and a signed consent form was obtained from each patient before the procedure. None of the patients were on systemic steroid therapy or antibiotics. Patients who were previously diagnosed with sarcoidosis and received treatment or were under follow-up were excluded. Stage 0 patients were also excluded.

Assessment

The demographic characteristics of the patients were recorded. Chest X-ray images and computed tomography (CT) scans were obtained. The presence of hilar and mediastinal lymphadenopathy and extrapulmonary lymphadenopathy (LAP) were noted. Patients with suspected extrapulmonary sarcoidosis by clinical and laboratory findings were evaluated for extrapulmonary involvement. Serum angiotensin-converting enzyme (ACE) levels, 24-h urinary Ca^{+2} output, tuberculin skin test (TST), and pulmonary function test (PFT) results were also recorded. The findings of PFT used to identify obstructive and restrictive lung diseases were normal. Based on chest X-ray radiological findings, patients were staged as 0: No radiographic abnormality (adenopathy or infiltrates), I: bilateral hilar adenopathy without interstitial parenchymal infiltrates, II: bilateral hilar adenopathy with interstitial parenchymal infiltrates, III: interstitial parenchymal infiltrates without hilar adenopathy, and IV: pulmonary fibrosis [1]. Radiologic staging was performed according to chest computed tomography findings.

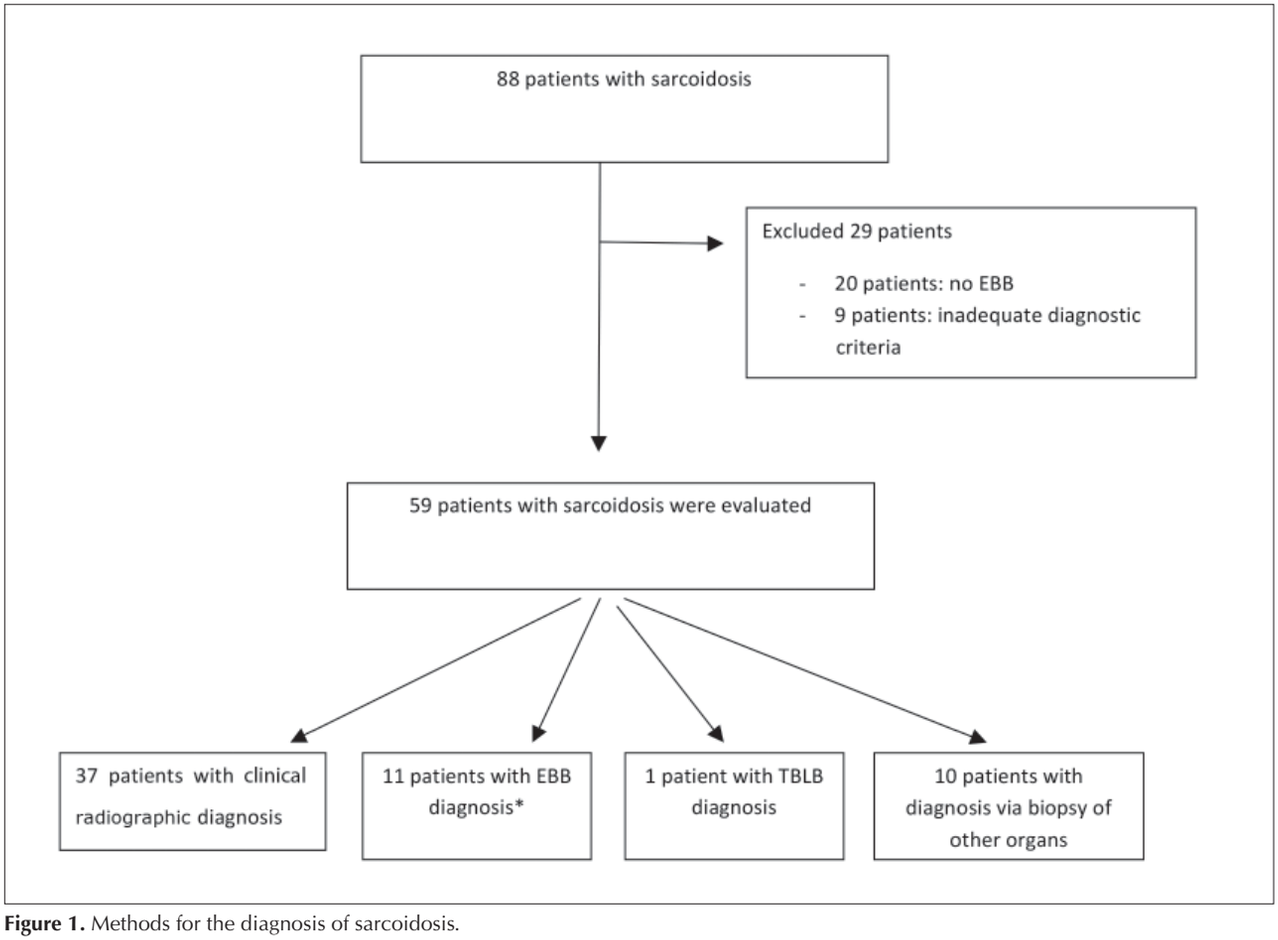

Figure 1. Methods for the diagnosis of sarcoidosis.
*The pathologic diagnosis was done with both EBB and TBLB in one patient.
EBB: endobronchial biopsy; TBLB: transbronchial lung biopsy.

Bronchoscopy

Fiberoptic bronchoscopy was performed under local anesthesia with midazolam and lidocaine. Bronchoalveolar lavage (BAL) was performed in the right middle lobe using 20 cc portions of sterile saline with a total amount of 120 cc. Patients with left lung involvement underwent BAL through the left lingula. TBNA was performed with a 22-gauge needle in patients with mediastinal and hilar LAP, when present in the CT scan. Afterwards, transbronchial lung biopsies were performed in parenchymal involvement areas. Two to four EBB specimens were taken from the abnormal mucosae; if abnormal bronchoscopic findings were not present, two to four additional EBB specimens were taken from the main carina and right middle-lower lobe carinas. FOB findings were classified as a: normal, b: blunt carina, c: extrinsic compression, d: endobronchial lesion, e: submucosal involvement, and f: hypervascularity. TBLB and TBNA could not be performed in all patients due to high complication rates, patient unwillingness, incompliance or procedure-related hypoxia. CD4/CD8 ratio was not studied in a group of patients due to the unavailability of laboratory facilities.

Diagnostic Criteria

The pathological diagnostic criterion was the presence of non-caseating epitheloid cell granulomas in biopsy specimens taken during FOB. In patients with clinical and imaging findings compatible with sarcoidosis without non-caseating epitheloid cell granulomas, positive diagnostic criteria were as follows: a: bilateral hilar LAP, b: elevated serum ACE and 24-hour urinary Ca^{+2} output, c: negative tuberculin skin test (TST), d: lymphocytic alveolitis or increased CD4/CD8 lymphocytes. These patients were included in the group in which diagnoses were based on clinical and radiological data.

The histopathological examination of bronchoscopic specimens eliminated the presence of tuberculosis in these patients by microbiological inspection.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences 15.0 (SPSS, Inc., Chicago, USA). Descriptive data were expressed as median with range or mean with standard deviation, according to the distribution of the parameters. Disease stage, extrapulmonary involvement, FOB findings, BAL lymphocyte predominance, CD4/CD8 ratio of ≥ 3.5 and blood ACE levels were compared with EBB. The chi-square test was used and p values < 0.05 were considered to be statistically significant.

RESULTS

Fifty-nine patients who were diagnosed with sarcoidosis were evaluated between January 2005 and October 2012. Forty-eight patients (81.4%) were females and 11 (18.6%) were males. The mean age was 45.9 ± 11.2 (range 24 to 66) years. Forty-four patients (74.6%) were housewives. Clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics of the patients

		n (%)
TST	Not yet	11 (18.6)
	Anergic	37 (61.7)
	to 10 mm	4 (6.8)
	11 to 15 mm	1 (1.7)
	> 15 mm	6 (10.2)
Pulmonary function test	Not yet	19 (32.2)
	Normal	30 (50.8)
	Obstructive disorder	4 (6.8)
	Restrictive disorder	6 (10.2)
Disease stage	I	18 (30.5)
	II	38 (64.4)
	III	2 (3.4)
	IV	1 (1.7)
Others organ involvement	No involvement	33 (55.9)
	Erythema nodosum	20 (33.9)
	Uveitis	4 (6.8)
	Other	2 (3.4)
Serum ACE level	Not yet	18 (30.5)
	Normal	13 (22.0)
	Abnormal	28 (47.5)
24-h urinary Ca+2	Not yet	43 (72.9)
	Normal	14 (23.7)
	Abnormal	2 (3.4)
Diagnostic methods	Clinico-radiographic	37 (62.7)
	EBB	11 (18.6)
	TBLB	1 (1.7)
	Other organ biopsy	10 (16.9)

TST: tuberculin skin test; ACE: angiotensin-converting enzyme; EBB: endobronchial biopsy; TBLB: transbronchial lung biopsy.

All patients underwent FOB. Thirty-nine (66.1%) had normal bronchoscopic findings, while EBL was observed in 5 patients. These five patients were all in stage II. BAL was performed in all 59 patients. CD4/CD8 ratio was studied in 44 patients. Ten patients underwent TBLB, while 46 underwent TBNA. EBB was performed in all 59 patients. The bronchoscopic findings of the patients are presented in Table 2. No complications related to the diagnostic procedures were observed.

Twenty-two patients (37.2%) were diagnosed with sarcoidosis according to the pathological examination. The diagnosis was based on EBB (non-caseating granulomatous inflammation) in 11 patients (18.6%), including EBB plus TBLB in one patient (1.6%), TBLB

Table 2. Bronchoscopic findings of the patients

		n (%)
FOB findings (n= 59)	No abnormality	39 (66.1)
	Blunt main carina	6 (10.2)
	Extrinsic compression	7 (11.9)
	Endobronchial lesion	5 (8.5)
	Submucosal involvement	1 (1.7)
	Hypervascularity	1 (1.7)
Findings supporting sarcoidosis in BAL (lymphocytic alveolitis or increased CD4/CD8 lymphocytes) (n= 59)	Yes	48 (81.4)
	No	11 (18.6)
Diagnosis with EBB* (n= 59)	Normal bronchial mucosa	33 (55.9)
	Non-caseating granulomatous inflammation	11 (18.6)
	Inflammatory alterations	15 (25.4)
Diagnosis with TBLB *(n= 10)	Yes	2 (20)
	No	8 (80)
CD4/CD8 ratio (n= 44)	≥ 3.5	37 (84.1)
	< 3.5	7 (15.9)
Lymphocyte rate (n= 59)	≥ 13	37 (62.7)
	< 13	22 (37.3)

* The pathologic diagnosis was done with both EBB and TBLB in one patient. FOB: fiberoptic bronchoscopy; BAL: bronchoalveolar lavage; EBB: endobronchial biopsy; TBLB: transbronchial lung biopsy.

alone in one patient (1.6%), and pathological specimens from other organs in 10 patients (16.9%). In the remaining 37 patients (62.75%), the diagnosis was based on clinical and radiological findings (Figure 1).

Among the 39 patients with normal bronchoscopic findings, 6 patients (15.3%) had a pathological diagnosis by EBB. The diagnosis was based on EBB in 5 of 20 patients (25%) with abnormal bronchoscopic findings (endobronchial lesion in 3 and mucosal abnormality in 2). However, normal or abnormal bronchoscopic findings did not affect the diagnostic accuracy of EBB (p= 0.369). There was no statistically significant relationship between the diagnostic accuracy of EBB and disease stage, extrapulmonary involvement, FOB findings, lymphocytic alveoli in BAL (≥ 13%), CD4/CD8 ratio of ≥ 3.5, and serum ACE level (p> 0.05). The characteristics of the patients who were diagnosed by EBB are shown in Table 3. There was no statistically significant difference in pulmonary function tests between patients with normal or abnormal bronchoscopic findings (p= 0.166).

The cell distribution of BAL revealed lymphocyte percentages greater than 13 in nine patients (81.8%). Nine patients (100%) in whom CD4/CD8 was studied had a ratio of ≥ 3.5, whereas seven of nine patients (77.7%) in whom serum ACE level was measured had increased levels (Table 3).

Pathological examination of the EBB specimens showed inflammation in 15 patients (25.4%). Nine of these patients (60.0%) were in stage II. Inflammatory alterations in EBB specimens were not associated with disease stage, extrapulmonary involvement, FOB findings, CD4/CD8 ratio of ≥ 3.5, and serum ACE level (p> 0.05).

No statistically significant relationship was observed between disease stage and extrapulmonary involvement, FOB findings, non-caseating granulomatous inflammation in EBB specimens, elevated lymphocyte percentage in BAL (≥ 13%), CD4/CD8 ratio of ≥ 3.5, and serum ACE level (p> 0.05).

Table 3. Characteristics of patients who were diagnosed by EBB*

Disease stage	Other organ involvement	FOB findings	Lymphocyte rate (%)	CD4/CD8 ratio	ACE level	PFT
II	No	EBL	≥ 13	11.00	Abnormal	Restriction
II	No	EBL	< 13%	-	-	Normal
I	No	No abnormality	≥ 13	6.00	Normal	-
II	No	Extrinsic compression	≥ 13	17.8	-	Obstruction
II	No	No abnormality	≥ 13	4.00	Abnormal	Normal
I	No	No abnormality	≥ 13	-	Abnormal	-
II	No	Blunt carina	≥ 13	12.30	Abnormal	Normal
II	Uveitis	EBL	< 13	4.00	Normal	Normal
II	Uveitis	No abnormality	≥ 13	-	Abnormal	Restriction
II	Erythema nodosum	No abnormality	≥ 13	4.49	Abnormal	Obstruction
II	Erythema nodosum	No abnormality	≥ 13	22.00	Abnormal	Normal

* p> 0.05, Pearson chi-square. EBB: endobronchial biopsy; FOB: fiberoptic bronchoscopy; ACE: angiotensin-converting enzyme; PFT: pulmonary function test; EBL: endobronchial lesion.

DISCUSSION

The diagnostic ratio of EBB has been reported in a wide range for patients with sarcoidosis [3,4,6-9]. This study aimed to investigate the additional diagnostic value of EBB in the diagnosis of pulmonary sarcoidosis. We found the diagnostic accuracy of this technique to be 18.6%. Kiter et al. [8] reported a 50% diagnostic accuracy for EBB, which was considered to be related to the multicenter and retrospective nature of their study. Also, Navani et al. [4], Bjemer et al. [6] and Kieszko et al. [9] diagnosed 11%, 45%, and 40% of their study patients by EBB, respectively [4,6,9]. In another study, in which the majority of patients (64.7%) were Afro-American, Shorr et al. [7] reported that the diagnostic ratio of EBB was 61.8% with an additional diagnostic value of 20.6%. In a multicenter study by Tournoy et al. involving 137 patients with a preliminary diagnosis of sarcoidosis, [3] a total of 121 patients underwent FOB, and a definitive diagnosis was achieved in 42% of these patients. The authors reported that the diagnostic ratios of TBLB, EBB, and TBNA were 54%, 20%, and 31%, respectively.

Although normal bronchial mucosa can be seen in sarcoidosis patients, airway abnormalities have been reported in up to 60% of patients [10]. These abnormalities include mucosal hyperemia or edema, bronchial distortion, bronchial constriction, and granulomas and ulcerations [10]. Shorr et al. [7] found normal airways in 29.4% of patients, while Kiter et al. [8] reported that 37.1% of patients had no airway abnormality, as confirmed by FOB.

In our study, we found normal bronchial mucosa in 39 patients (66.1%). However, we observed abnormal mucosal findings in 33.9% of patients. There was no statistically significant relationship between positive EBB results and normal or abnormal airway anatomy. On the other hand, Shorr et al. [7] observed a significant correlation between positive EBB results and normal or abnormal airway anatomy (p= 0.014). The authors also reported positive EBB results in 75% of patients with abnormal airway anatomy. However, they did not differentiate endobronchial lesions and granulomas. These results can be greatly attributed to the race of the subjects.

Ishii et al. [11] performed TBLB, BAL, and EBB in 18 Japanese patients who were primarily suspected to have sarcoidosis with bronchoscopic normal mucosa findings. The diagnostic ratios of TBLB and EBB were 61.1% (n=11) and 5.5% (n=1), respectively. The authors observed pulmonary involvement in all patients, as confirmed by CT and BAL; however, none of the patients had FOB-related complications. Extrapulmonary involvement was also seen in five patients. The authors concluded that EBB in combination with TBLB did not improve the diagnostic ratio in sarcoidosis patients with normal bronchial mucosae. Pulmonary sarcoidosis with endobronchial involvement was attributed to the race of the subjects. In another study, Shorr et al. [7] reported that the diagnostic ratio of EBB was 30% in patients with normal bronchial mucosae and higher in patients with abnormal bronchial mucosae. In addition, Torrington et al. [12] reported a 2.2 fold higher ratio for the diagnosis of sarcoidosis in Afro-Americans using EBB. Burke et al. [13] reported that a higher diagnostic ratio of EBB was associated with increased granuloma density of bronchial and lung tissues in this patient population. In our study, we achieved a pathological diagnosis of sarcoidosis in 15.3% of patients (n=6/39) with normal bronchial mucosae as assessed by FOB, based on the EBB specimens and the presence of non-caseating granulomas. Differences in the diagnostic ratios of EBB across these studies may be explained by the sample sizes and by the races of the participants.

In our study, pathological examination of the EBB specimens showed inflammatory alterations in 25.4% of patients (n= 15). Despite the lack of non-caseating granulomas, this finding supports the presence of inflammation in sarcoidosis patients. However, this finding alone does not allow us to achieve a pathological diagnosis. In addition, biopsy specimens were likely to be taken in the adjacent sites of granuloma in these patients.

The CD4/CD8 ratio was ≥ 3.5 in all patients who were diagnosed through EBB, while 81.8% of patients had lymphocyte rates of ≥ 13% in BAL and 77.7% of patients had elevated serum ACE levels. These results thus suggest that laboratory test results are supportive for sarcoidosis; however, EBB is useful in the diagnosis of patients with normal bronchial mucosae.

Pulmonary sarcoidosis may be accompanied by obstructive or restrictive lung diseases in a varying range. Granulomatous lesions and bronchial constriction by lymph nodal compression may lead to obstructive lung disease, whereas pulmonary parenchymal disease may result in restrictive lung disease [10]. In our study, 10% of patients (n= 40) had obstructive lung disease, while 15% (n= 40) had restrictive lung disease, as assessed by PFT. There was no relationship between radiological staging and PFT variables. No significant difference in PFT variables was observed among patients with normal or abnormal bronchoscopic findings. A Case Control Etiologic Study of Sarcoidosis (ACCESS) trial demonstrated that 14% of patients had obstructive lung disease, while 30% had restrictive disease patterns [14]. Kieszko et al. [9] found abnormal PFT results in more than half of the patients with EBB positivity. Bjemer et al. [6] reported that the inflammatory activity ratio was higher in European patients with sarcoidosis and that bronchial involvement may worsen the clinical course of the disease, leading to an increased incidence of pulmonary dysfunction. Consistent with these findings, 4 of 11 patients (36.3%) diagnosed with EBB had abnormal PFT results in our study.

No significant relationship between disease stage and positive EBB results was observed. However, the diagnostic ratio of EBB was higher (23.6%) among patients with stage II disease. Additionally, majority of the patients (81.8%)

who underwent EBB were in stage 2 (n=9). The diagnostic ratio of EBB was lower (11.1%) in patients with stage 1 disease. In another study, Navani et al. [4] found stage II sarcoidosis in three of nine patients (33%). However, none of the patients (n= 18) with stage I were diagnosed using EBB. Only three patients (n= 27) with stage Iand stage II disease were diagnosed using EBB. The authors suggested that TBLB and EBB are used as an initial procedure in the diagnosis of pulmonary sarcoidosis. Similarly, studies that were conducted in Turkey reported the diagnostic ratios of EBB to be 45%, 50%, and 68% in patients with stage I, stage II, and stage III disease, respectively, indicating no additional diagnostic value when used in combination with TBLB [8].

The major limitation of the study was the lack of a comparative analysis between EBB and another bronchoscopic diagnostic technique, including TBLB. In addition, TBLB could not be performed in all patients for several reasons, including incompatible imaging findings, lack of cooperation, patient's unwillingness, and procedure-related complications such as bleeding and pneumothorax. Another limitation was the absence of a pathological diagnosis, although we performed TBNA in 46 patients. The diagnosis rate was 23.9% (11 of 46 patients) for patients who were undiagnosed by TBNA but who underwent EBB. This may be explained by inadequate specimen collection and the absence of a cytologist in our center.

In conclusion, despite the introduction of novel bronchoscopic techniques, standard FOB is the primary diagnostic tool for sarcoidosis patients. EBB not only offers the advantages of a high diagnostic ratio in patients with mucosal abnormalities but also contributes to pathological diagnosis in patients with normal bronchial mucosae. Our study results also suggest that EBB improves the diagnostic ratio in sarcoidosis, even in the presence of normal bronchial mucosae. We thus recommend that for patients without evidence of parenchymal findings who do not accept TBLB and who are undiagnosed by TBNA, EBB may be used to support the diagnosis, with a low complication rate, for patients undergoing FOB with a preliminary diagnosis of sarcoidosis in healthcare centers where EBUS is not available.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ministry of Health Clinical Research Ethics Committee in Manisa.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.G., P.Ç., A.Ö.A.; Design - T.G., P.Ç., A.Ö.A.; Supervision - P.Ç., A.Ş.C., Y.H.; Resources - T.G., A.Ö.A., Y.H., A.I.; Materials - A.I., T.G., Y.H.; Data Collection and/or Processing - T.G., Y.H., A.I.; Analysis and/or Interpretation - T.G., P.Ç., A.I.; Literature Search - T.G., P.Ç., A.Ö.A.; Writing Manuscript - T.G., P.Ç., A.Ö.A.; Critical Review - A.Ş.C., A.Y., P.Ç.; Other - A.Y., A.Ş.C., P.Ç.

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CASE REPORT

A Case of Idiopathic Subglottic and Bilateral Bronchial Stenosis

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Abstract

Subglottic stenosis is rarely idiopathic. In this case report, a 40-year-old female patient presented with subglottic stenosis with an unidentified etiology along with bilateral bronchial stenosis. Hoarseness arose in the last 4 years in this patient, who was undergoing treatment because of asthma for 13 years. Her physical examination revealed the presence of bilateral rhonci. Her tomography analysis revealed tracheal stenosis in a 2-cm segment at the C6-7 level. Her bronchoscopy analysis revealed subglottic stenosis. White plaques were observed in the entire tracheobronchial tree; biopsy was performed and lavage was taken. Samples were sent for pathological and microbiological examinations. Stenosis in the bronchial system was clear in the left main bronchus entry and at the right intermediate bronchus level. Dilatation was performed. Chronic active inflammation and squamous hyperplasia were observed in the pathology of the biopsies. Growth did not occur in tuberculosis and nonspecific cultures. Reflux was not present in the gastrointestinal system examination. All serological and rheumatologic examinations performed were normal. Idiopathic subglottic stenosis is exceedingly rare. Bronchial system stenosis accompanying idiopathic tracheal stenosis is even rarer, and its treatment is difficult.

KEY WORDS: Bronchial stenosis, idiopathic tracheal stenosis, idiopathic bronchial stenosis, subglottic stenosis, tracheal stenosis

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INTRODUCTION

The general causes of tracheal stenosis are intubation, tracheostomy, chemical or basic damage, and trauma. Rarer, inflammatory diseases such as Wegener's granulomatosis (WG), connective tissue diseases, and sarcoidosis can play roles in the etiopathogenesis. When all these causes are excluded, the diagnosis is idiopathic subglottic stenosis (ISS) [1]. ISS is a very rare disease, more commonly observed in women. In this study, an ISS case that constituted a difficulty in treatment because of diffuse stenosis in both bronchial systems accompanying subglottic stenosis is presented.

CASE PRESENTATION

A 40-year-old female patient who was undergoing treatment for asthma underwent appendectomy 9 years ago. Prolonged intubation was not present. Hoarseness started in the last 4 years, nose bleeding occurred 2 weeks ago, and she was evaluated by an ear, nose, and throat expert. Sinusitis and nasal crusts were observed in the patient. After a recurrence of nose bleeding, indirect laryngoscopy was performed, and "stenosis in the subglottic area" was observed and she was directed to our polyclinic.

Bilateral rhonchus and stridor were present in her physical examination. Sedimentation and C-reactive protein values were normal in her blood analyses. There were no features in her chest radiography.

In the respiratory function test, FVC was measured as 3.48 l (71%), FEV_1 as 3.01 l (65%), and FEV_1/FVC as 87%. In her cervical and thoracic computed tomography, tracheal stenosis was observed in the narrowest part of an approximately 2-cm segment at the C6-7 level, with a coronal diameter of 7.7 mm and a sagittal diameter of 12.1 mm (Figure 1). Endobronchial lesion was not detected. Subsegmental linear atelectasis appearance was present in the lower left pulmonary lobe.

Fiberoptic bronchoscopy was performed to the patient with a provisional diagnosis of subglottic stenosis, as a way of planning prior to the surgical intervention. Stenosis that proceeded for subglottic 2-cm segment was observed in the

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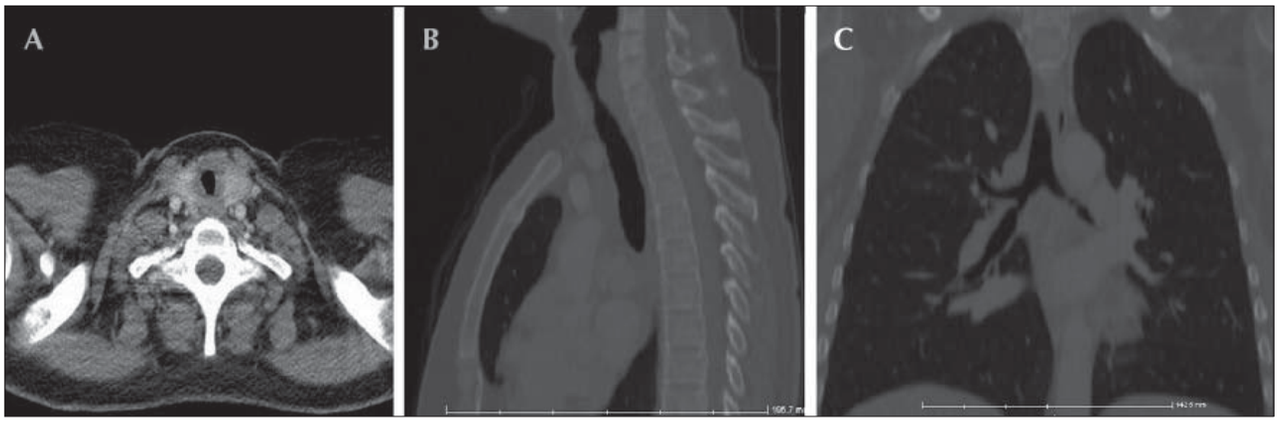

Figure 1. Thoracic CT sections. (a) Stenosis in the subglottic region in the transverse section. (b) Stenosis in the sagittal section is observed to be on a segment that is approximately 2 cm long. (c) Stenosis is observed in the left main bronchus in the coronal section.

fiberoptic bronchoscopy (Figure 2). Diffuse white plaques that occasionally caused webs were observed in the entire tracheobronchial tree. Stenosis in the bronchial system was clear in the left main bronchus entry and at the right intermediate bronchus level (Figure 2). Because of diffuse stenosis, surgical intervention was abandoned, and rigid bronchoscopy was performed in the same session. Biopsy was performed in stenosis areas and lavage was taken. Samples were sent for pathological and microbiological examinations. Dilatation was performed upon noticing, during rigid bronchoscopy, that the stenosis was not very stiff. The pathology of biopsy and lavage was reported as "chronic active inflammation and squamous hyperplasia." Growth did not occur in tuberculosis and nonspecific cultures. Mycobacteria polymerase chain reaction (PCR) studies were negative. Microorganisms were not observed in Gram staining, and fungal spores and hyphae were not observed in periodic acid-Schiff staining.

When the tomography of the patient was uploaded to the three-dimensional software and retrospectively re-examined, stenosis was observed in the bronchial systems as well in the coronal sections (Figure 1c).

Reflux was not present in the gastrointestinal system examination. Serological and rheumatologic examinations [anti-nuclear antibody (ANA)= negative, cytoplasmic anti-neutrophil antibody (c-ANCA)= negative] did not return any pathological findings.

The complaints of the patient with respect to shortness of breath increased 6 months after bronchoscopic dilatation, and dilatation was performed again with rigid bronchoscopy, and mitomycin C attachment was performed. The patient developed complaint of hemoptysis 15 days after the surgery, and she was hospitalized and followed up for 2 days. During hospitalization and later follow-ups, hemoptysis complaints did not arise. The patient is being followed up without symptoms on the 8th month of the 2nd bronchoscopic dilatation. Written consents for every intervention performed were obtained from the patient. The obtained written consents included the potential scientific and educational use of the findings and images regarding her disease.

DISCUSSION

The most frequent causes of tracheobronchial system stenoses are intubation and tracheostomy. ISS is quite rare. In the study of Rubikas et al. [2] consisting of 75 laryngotracheal patients, only one patient's diagnosis was ISS, and the cause of stenosis of 71 patients was intubation. The physiopathology is not known in ISS; however, some authors claimed that gastroesophageal reflux, chronic coughing, and abnormal estrogen response can have influences [3]. On the other hand, its relationship with WG is emphasized in many studies and cases. It is reported that as much as 49% of the patients are diagnosed with ISS because of the absence of WG findings and symptoms [4]. There are even cases that were diagnosed as WG 20 years after the ISS diagnosis [5]. The case was examined for WG, and WG diagnosis was excluded. Nevertheless, her follow up continues in light of the literature.

The treatment of ISS is controversial because it is rarely seen and its physiopathology is unclear. Surgical treatment is still the first treatment choice, with success rates as high as 90% in subglottic stenoses associated with a benign factor [6]. Marcillo et al. [3] reported a 97% success rate with surgical correction in a study consisting of 64 cases with diagnoses of ISS. Endoscopic treatments are reported as good for palliation and as progressing with frequent recurrences in the long run [7]. There are also authors, most of which report achieving sufficient results with endoscopic treatment [8]. The type the endoscopic treatment methods to be performed is a controversy. Mitomycin C application is frequently recommended in endoscopic applications [6]. Stent applications added to dilatation will yield longer palliation in the patient, and it can establish patient's comfort without the need of tracheostomy or more invasive processes [9]. Radiological and clinical findings of the patient made us consider ISS; therefore, surgical treatment was planned following bronchoscopic evaluation. However, bronchoscopy revealed that the patient not only had ISS but also bronchial stenoses. She therefore differed from the cases previously reported in the literature. Surgical treatment was not possible in our patient, and we performed bronchoscopic dilatation in the first admittance. In the second admittance, mitomycin C was administered alongside dilatation. Mitomycin C is an antineoplastic agent

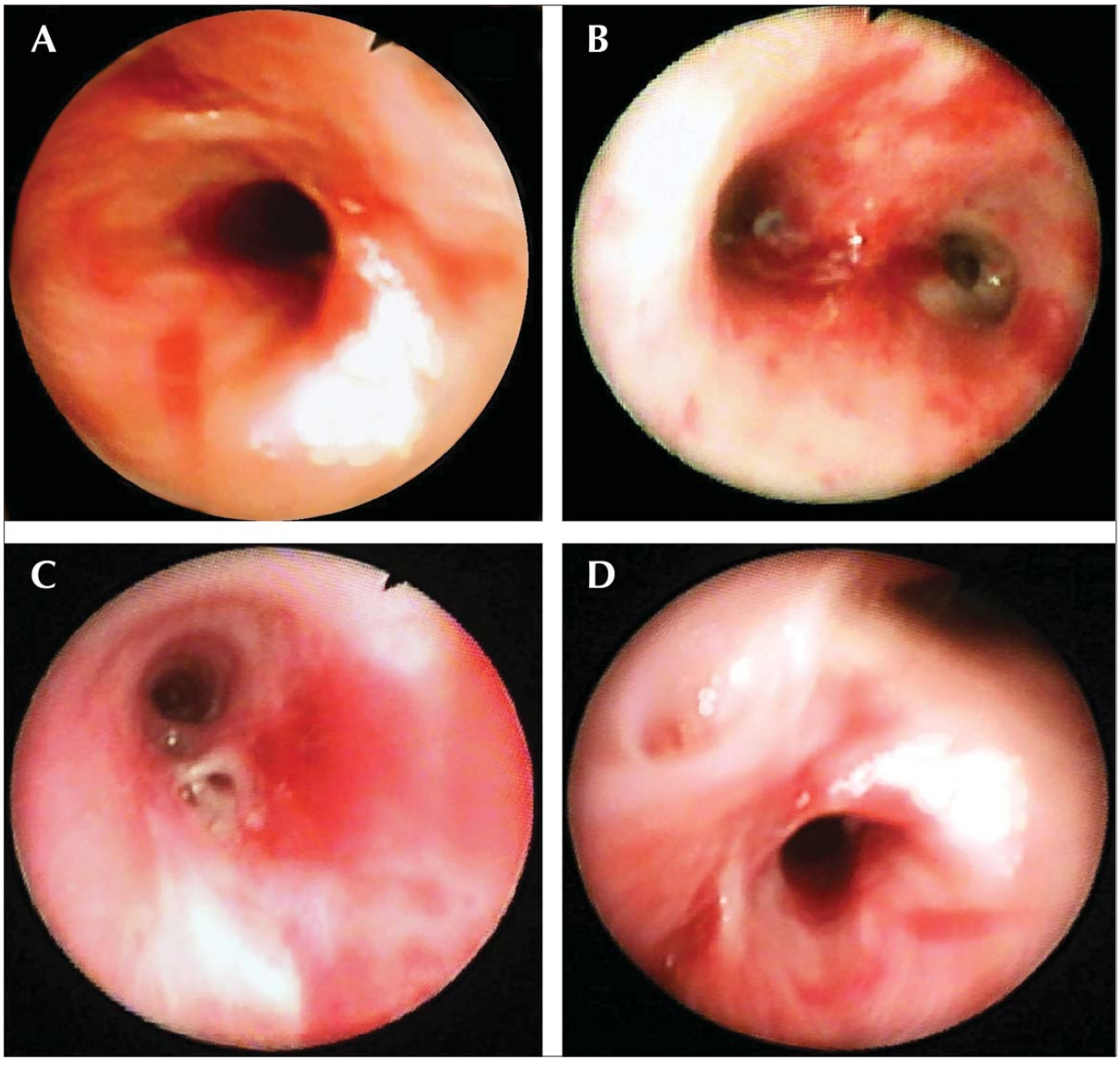

Figure 2. Bronchoscopic images. (a) Stenosis in the subglottic level. (b) Appearance in the carina level. (c) Stenosis in the left main bronchus. (d) Stenosis in the right intermediate bronchus.

that inhibits fibroblast proliferation and modulates wound healing [10]. Good results of its application as a support for endoscopic treatment in trachea stenoses are reported [10]. The case was particularly observed to benefit from the second dilatation (one where mitomycin C was performed). In the retrospective, radiological examination, in addition to the initial evaluation of radiologists, stenoses are observed in the left main bronchus as well in the coronal sections (Figure 1c). We maintain that although the treatment plan of tracheal diseases is being formed, it is crucial that the detailed radiological examinations are conducted by radiology experts who are experienced in this subject.

Surgical correction is the first choice in cases of airway stenoses associated with a benign factor, if an emergency response is not required [6,8]. This case was not suitable for surgical treatment because of diffuse airway involvement. Dilatation is an important treatment choice in patients with submucosal or extrinsic lesions where curative surgery is not possible [8]. Similarly, dilatation is the first choice in cases with submucosal or extrinsic lesions who require an emergency response, and stent is recommended in suitable patients [8]. Mechanical dilatation can provide sufficient treatment, particularly in cases with web-style ISS [1]. Bronchoscopic, radiological, and pathological findings of the case made us consider a submucosal-type stenosis, and no finding was detected regarding cartilaginous type-stenosis. Therefore, we maintain that the case benefited, at least partially, from dilatation. Because of diffuse airway stenosis and the complexity of stenosis localizations, we initially did not consider stent application in our case. Stent application can be considered as a treatment option if stenosis recurs in our patient who is being followed up. In cases with cartilaginous-type stenosis or with an exophytic lesion, curating with

dilatation and endobronchial treatment modalities (laser, electrocautery, cryotherapy, photodynamic treatment etc.) are recommended [8]. Furthermore, surgical treatment procedures can be performed depending on the etiological and pathological cause [2]. Endobronchial treatment modalities (preferably laser, because it is responsible for less mucosal damage) can be used in cases with submucosal stenosis in whom dilatation cannot be achieved via conventional methods (such as balloon and bougienage) [8]. Endobronchial treatment modalities were not required in our case where sufficient airway patency was established via mechanical dilatation. Stent was not considered because of the diffusiveness of the lesions.

Idiopathic subglottic stenosis is a rare condition, and there is no consensus regarding its treatment. Because of its slow progression, patients can undergo asthma treatment by mistake for a long time. We tried to administer endoscopic treatment in our case that differed from other ISSs due to diffuse stenosis in the tracheobronchial system. We assume that, in tracheobronchial system stenoses, one must develop a treatment strategy on a case-by-case basis and choose a treatment that is specific to the case.

Informed Consent: Written informed consent was obtained from the patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ü.A., G.Y.; Design - Ü.A., F.T.; Supervision - G.Y.; Data Collection and/or Processing - Ü.A.; Analysis and/or Interpretation - Ü.A., F.T., G.Y.; Literature Review - Ü.A., F.T.; Writer - Ü.A.; Critical Review - F.T., G.Y.

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

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CASE REPORT

Flexible Fiberoptic Bronchoscopy Through the Laryngeal Mask Airway in a Small Premature Infant

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Abstract

Flexible bronchoscopy (FB) can be used safely for wider indications in children. Ultra-thin bronchoscopes are used for premature or newborn infants and are of limited diagnostic value. Bronchoscopes with a suction channel, may lead to problems when the nasal passage is narrow, particularly in patients under 2.5 kg. In addition, it may cause bronchospasm and hypoxia in small infants during the procedure because of an almost complete obstruction of the airway. A laryngeal mask airway (LMA) may prevent both bronchospasm and hypoxia because it does not need a nasal route. In addition, the LMA allows positive pressure ventilation during the procedure. We performed FB with a 3.7 mm bronchoscope through the LMA in a 75-day-old and 1910 g premature baby with atelectasis. This is the first and successful FB experience in such a small premature infant reported in the literature using a 3.7 mm bronchoscope through the LMA.

KEY WORDS: Child, flexible bronchoscopy, laryngeal mask airway

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INTRODUCTION

Flexible endoscopy of pediatric airways was first reported in 1978. Since then, the technique has continued to develop, and the number of flexible bronchoscopy (FB) procedures in pediatric patients has increased with the availability of smaller devices. FB in children of the age group of 0-18 years can be used safely for wider indications in children of different weights and ages. Pediatric airway bronchoscopy may involve the inspection of the nose, pharynx, larynx, trachea, and bronchi. Diagnostic indications include the evaluation of stridor, an unexplained or persistant wheeze or cough, possible malformations, recurrent atelectasis or infiltrations, hemoptysis, and collection of specimens. No certain contraindications for bronchoscopy were noted [1]. The laryngeal mask airway (LMA) has been used since 1983, and the use of bronchoscopy via the LMA of infants and children has increased with the availbility of smaller sizes of the LMA [2]. We performed FB with a 3.7 mm bronchoscope via the LMA in a 75-day-old 1910 g premature baby with atelectasis. This is the first and successful FB experience in such a small premature infant reported in the literature using a 3.7 mm bronchoscope through the LMA.

CASE PRESENTATION

A 75-day-old male baby weighing 1910 g was referred to our clinic for examination of recurrent atelectasis. He was born at a gestational age of 28 weeks weighing 1160 g. He exhibited symptoms of having respiratory distress syndrome at birth, and was immediately intubated in the operating room and then transfered to the intensive care unit. In addition, anemia, hypoglycemia, and recurrent pneumonia were also appropriately treated. He had several extubations and intubations due to the recurrent atelectasis after extubations. He needed mechanical ventilation because he could not tolerate the extubation. He was referred to our bronchoscopy unit for recurrent atelectasis in the same area. Chest X-ray revealed atelectasis in the right upper lobe.

The patient's consent was taken from the parents. The infant had been brought to our clinic in a transport incubator intubated with a 3.5 mm internal diameter tracheal tube. Mechanical ventilation was necessary; oxygen saturation was 96%. He was looking well and very comfortable under mechanical ventilation; however, chest auscultation revealed different breath sounds throughout the left and right lung. Laboratory studies did not indicate any infectious disease.

At adequate room temperature and after having applied the routine anesthesia monitoring standards, FB was performed to evaluate the respiratory airways. The internal diameter of the endotracheal tube was not sufficient to allow the use

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of a bronchoscope, thus necessitating mechanical ventilation and withdrawal of the endotracheal tube. An anesthesiologist induced anesthesia using 0.1 mg of atropine and 0.1 mg/kg of midazolam for premedication, 1 mg/kg of propofol, and 1 mg/kg of cetamine. A size 1 LMA was inserted successfully and ventilation (manually assisted) was non-problematic. The FB was performed by a pediatric pulmonologist. The LMA could be used as a conduit both for a bronchoscope and mechanical ventilation with a rubber valve-fitted opening of an angle piece attached to the outer aperture of the LMA (Figure 1). We used an FVB with an outer diameter of 3.7 mm (Pentax EB-1170K, Hoya Corporation, Tokyo, Japan).

Examination of the patient revealed severe edema of the vocal cords. Sixty percent of the lumen was obstructed by residual granulation tissue in the subglottic region (Figure 2a). After passing the obstruction, nodular, fragile, and hyperemic mucosa was seen throughout the trachea and carina. The anatomic structure of the carina was lost. Granulation tissue and nodular formations obstructed up to 80% of the lumen of the bilateral main bronchus (Figure 2b). Viscous secretions were aspirated and the bronchoscope could not be passed through the obstruction. The patient was hemodynamically stable and no complication was noted. The patient was then reintubated and transferred to the intensive care unit.

DISCUSSION

Pediatric FB is used for ever wider indications of children's respiratory problems and complications; however, the decision to perform FB in children should always be made on an individual basis after consideration of a patient's characteristics. Stridor or noisy breathing is the most common indication in infants, whereas the evaluation of airway obtruction, which may involve the upper or lower airway or both, is the most common indication for FB in children [3]. According to Barbato et al. [4], recurrent or persistant pneumonia, atelectasis, and wheezing that does not respond to therapy are the most common indications for FB in children. Our patient had recurrent atelectasis and could not be extubated because of it.

Bronchoscopes of varying diameters are used in pediatric patients. Ultra-thin bronchoscopes offers new diagnostic opportunities, particularly to neonatologists [5]. Furthermore, ultra-thin bronchoscopes are of limited diagnostic value when excessive bronchial secretions obstruct the view of the working field because of the abscence of the suction channel. In addition, bronchoalveolar lavage cannot be evaluated, and these bronchoscopes cannot be used theurapeutically in some cases such as atelectasis. In the literature, the youngest patient (a premature 1-week-old infant weighing 600 g) on whom an infant bronchoscope was used was part of a large FB series [6]. Nussbaum [6] used a 2.2 mm bronchoscope in preterm neonates and intubated infants where the small glottic or endotracheal tube size renders the 3.5 mm bronchoscope useless. He determined that a 2.2 mm bronchoscope was of limited value when excessive bronchial secretions obstructed the view of the working field because of the absence of a suction channel.

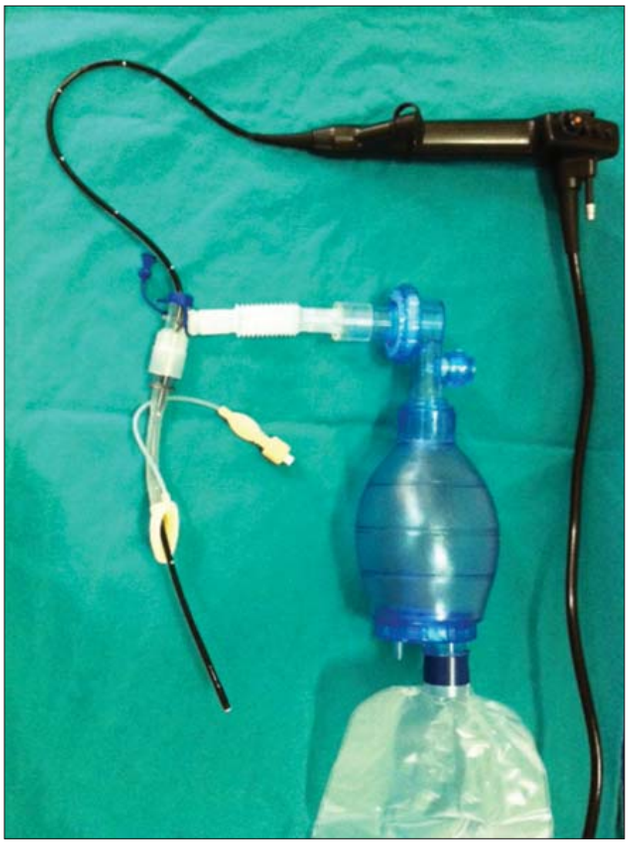

Figure 1. Using the LMA with a conduit for a bronchoscope [Diameter of 3.7 mm (Pentax EB-1170K, Hoya Corporation, Tokyo, Japan)] with a rubber valve-fitted opening of an angle piece attached to the outer aperture of the LMA.
LMA: Laryngeal mask airway.

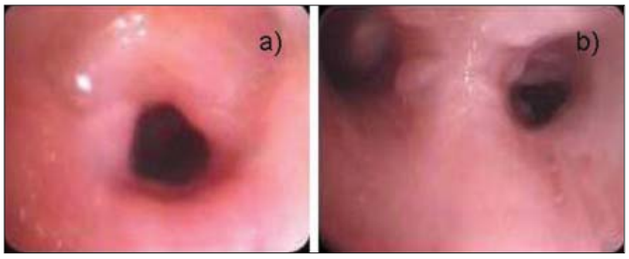

Figure 2. a, b. Obstruction of subglottic region up to 60% by residual granulation tissue (a). Anatomic structure of carina and obstruction of the lumen of the bilateral main bronchus up to 80% with granulation tissue and nodular formations (b).

Pediatric bronchoscopes with diameters of 2.8, 3.5, 3.7, and 3.8 mm have suction channels. The use of a bronchoscope with a suction channel, particularly in patients under 2.5 kg, may lead to problems when the nasal passage is narrow. In addition, it may cause bronchospasm and hypoxia in small infants during the procedure because it almost completely obstructs the airway. The LMA can prevent both bronchospasm and hypoxia because it does not need a nasal route beside allowing positive pressure ventilation during the procedure. Somri et al. [7] reported a bronchoscopy of a 2.2 kg neonate with a 3.3 mm bronchoscope via the LMA. Lan et al. [8] performed 24 FB with a 3.6 mm fiberoptic pediatric bronchoscope without using the LMA and reported that the youngest patient was a 4-day-old 1672 g baby. The usage of

3.6 mm or larger bronchoscopes is rare in small infants. We performed FB successfully with a 3.7 mm bronchoscope through the LMA in a 1910 g premature infant because of dense mucus plugs and atelectasis and no complication was encountered. This is the first case reported in the literature using a 3.7 mm bronchoscope through the LMA in such a small premature infant patient. Although 2.8 mm bronchoscopes may be more suitable for FB in such small infants, all sizes of bronchoscopes cannot be present in all units, particularly in developing countries. Moreover, no pediatric flexible bronchoscopy unit, except our unit, has a 2.8 mm flexible bronchoscope in Istanbul.

Larengeal mask airway is a safe and effective procedure for pediatric FB and allows the evaluation of the airway during the spontaneous ventilation. Nussbaum et al. [9] studied FB via the LMA in a group of children and concluded that the procedure had been well-tolerated in them and that no complication emerged. Naguib et al. [2] demonstrated in 1947 procedures that FB through the LMA rendered the lowest rate of overall procedure-related complications when compared to other routes (nasal or endotracheal entubation). The LMA may complicate the assessment of the upper airway abnormalities such as laryngomalacia as a disadvantage. To facilitate the procedure in children and infants who are intubated and ventilated, it may be necessary to alter the method of airway maintenance from an endotracheal tube to a laryngeal mask or a face mask because of an unsufficient diameter of the endotracheal tube for bronchoscopes. Based on their advantages and disadvantages, the LMA could provide a better airway than other conventional airways [10]; however, data are limited on the use of these devices in small, premature infants.

In conclusion, the LMA is a safe and effective route for pediatric FB. A 3.7 mm bronchoscope may be used through the LMA in small infants, particularly those who have atelectasis and viscous secretions. Additional cases of successful procedures are required to establish this method as a standard procedure in small infants.

Informed Consent: Written informed consent was obtained from the patient's parents who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.H.G., E.C.; Design - A.H.G., E.C., U.T.; Supervision - E.C.; Materials - A.H.G., U.T.; Data Collection and/or Processing - A.H.G.; Analysis and/or Interpretation - A.H.G., E.C., U.T.; Literature Review - A.H.G.; Writer - A.H.G., E.C.; Critical Review-E.C., U.T.; Other - A.H.G., E.C., U.T.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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CASE REPORT

New-Onset Sarcoidosis After Remission of Cushing's Syndrome

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Abstract

Exposure to high levels of endogenous or exogenous glucocorticoids suppresses the inflammatory response genes. Excessive endogenous hypercortisolism may mask the active inflammatory diseases. Rebound immune modulation may occur after Cushing's syndrome (CS) remission, leading to the new onset of autoimmune diseases. Here, we report a 27-year-old female patient who was recently diagnosed with sarcoidosis after remission of CS. Normal thorax imaging showed that the patient was free of disease during the course of CS and without any symptoms of sarcoidosis. After complete remission of CS, she was diagnosed with sarcoidosis based on clinical and radiological evidence. Excessive hypercortisolism may suppress the active inflammatory stage of sarcoidosis. However, the disease became apparent after the reduction of cortisol levels following the treatment of CS.

KEY WORDS: Sarcoidosis, Cushing's syndrome, hypercortisolism

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INTRODUCTION

Cushing's syndrome (CS) comprises a large group of signs and symptoms that reflect prolonged and inappropriately high exposure of tissue to glucocorticoids [1]. Endogenous or exogenous glucocorticoids suppress the inflammatory response; therefore, they are the most preferred treatment options in inflammatory diseases. Persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy [2]. Excessive endogenous hypercortisolism may mask the active inflammatory disease. Rebound immune modulation may occur after CS remission, thus leading to the new onset of autoimmune diseases that focus mainly on thyroid autoimmune diseases [2].

Sarcoidosis is a systemic inflammatory disease characterized by the presence of granulomatous inflammation in affected tissues. The peripheral lymph nodes, lungs, eyes, and skin are the most involved organs [3]. The etiology of the disease remains unknown. However, the prevailing hypothesis is that various unidentified, poorly degradable antigens of either infectious or environmental origin could trigger an exaggerated immune reaction in genetically susceptible hosts [4].

New-onset sarcoidosis after remission of CS is reported in few cases in the literature. Here, we report a case with new-onset sarcoidosis after complete remission of CS due to adrenal adenoma.

CASE PRESENTATION

A 27-year-old female was admitted to our hospital with a right adrenal adenoma that was discovered during examination for right flank pain. She had a history of hypertension for 3 years and complained of a 23-kg weight gain in 2 years. The patient was normotensive. She was treated with valsartan/hydrochlorothiazide (160 mg and 12.5 mg, respectively) once daily. She had no history of hypertensive spells and other past medical records. On physical examination, she had moon face with facial plethora, buffalo hump, acne, abdominal obesity with body mass index (BMI) 32 kg/m^2, purple abdominal stria, and easy bruising.

Laboratory evaluation revealed normal glucose levels, complete blood count, and liver and renal functions. Functional screening of the adrenal adenoma was performed to eliminate Conn's syndrome, Cushing's sydrome, and pheochromocytoma. Twenty-four hour urinary free metanephrine and normetanephrine levels were within normal limits. Plasma aldosterone/plasma rennin activity ratio was < 20 with normal serum potassium levels. She had high midnight serum cortisol levels (14 ug/dL), and the cortisol levels were not suppressed with two day 2 mg dexamethasone suppression test. Twenty-four hour free cortisol levels showed a 4-fold increase (1292 mg/dL), and Cushing's sydrome (CS) was diagnosed. Basal ACTH levels

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were < 5 pg/mL in three occasions, thus reflecting an adrenal-dependent cause.

Plain chest X-ray and computed tomography (CT) of the patient were normal (Figure 1a, 2a). Adrenal CT demonstrated right adrenal mass, which was 50 mm in diameter (Figure 3). It had clear margins in addition to its low density on CT, which were indicative of an adenoma. The patient underwent right adrenalectomy with corticosteroid coverage. The post-operative period was uneventful, and she was discharged with corticosteroid replacement. The pathology of the adrenal mass was a benign cortical adenoma.

The corticosteroid treatment reduced gradually and lasted till the end of the 18 month. During the last dose decrement, she started to complain of cough without sputum or fever. Physical examination of the respiratory system was normal. Chest X-ray revealed bilateral hilar and right paratracheal enlargement (Figure 1b). Bilateral hilar and mediastinal lymphadenopaties were present in the in thorax CT (Figure 2b). The biggest lymphadenopathy was nearly 3.5 cm in size at the subcarinal region. The serum calcium level was within normal limits. The tuberculin skin test result was 0 mm in the scar positive BCG vaccinated patient. The level of serum angiotensin converting enzyme was increased (178 U/L; normal range: 0-52 U/L). Carbone monoxide diffusion capacity (DLCO) was decreased (71%), while the pulmonary function test was normal. Fiberoptic bronchoscopy showed that main and right secondary carinas were edematous and the entry of the left upper lobe was narrowed by mucosal edema. Bronchoalveolar lavage (BAL) and fine needle aspiration were taken. Flow cytometric evaluation of the bronchoalveolar fluid showed lymphocytic alveolitis (17.1%). CD4/CD8 ratio was 6.71. The histopathological evaluation of the fine needle aspiration showed that there were noncaseous granulomas. The patient was diagnosed with sarcoidosis after the clinical, radiological, and histopathological evaluations. She will be followed up 3 months later with thorax CT for restaging. Corticosteroid treatment will be initiated if there is additional parenchymal involvement.

DISCUSSION

Endogenous CS is caused either by excess adrenocorticotropic hormone (ACTH) secretion or by autonomous cortisol release from the adrenal cortex. Glucocorticoids are the main endogenous mechanism to suppress the inflammatory response genes [2]. Exposure to persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy, thereby resulting in immunosuppression [5]. On the other hand, in post-stressful situations, transient rebound thymic hyperplasia may be observed in children and adolescents [5]. Similar situations may be observed after remission of CS of all types, which

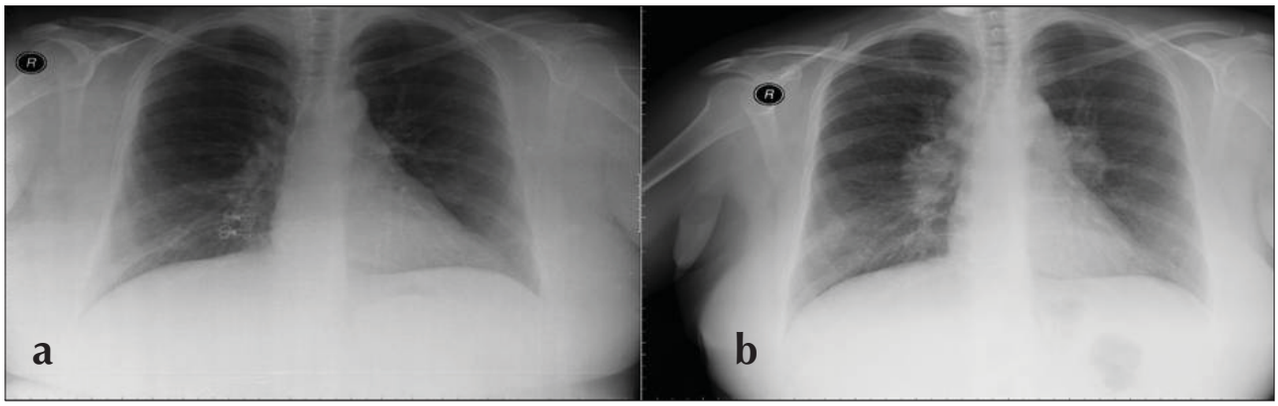

Figure 1. a, b. Plain chest X-ray of the patient: (a) before treatment of CS and (b) after treatment of CS.
CS: Cushing syndrome.

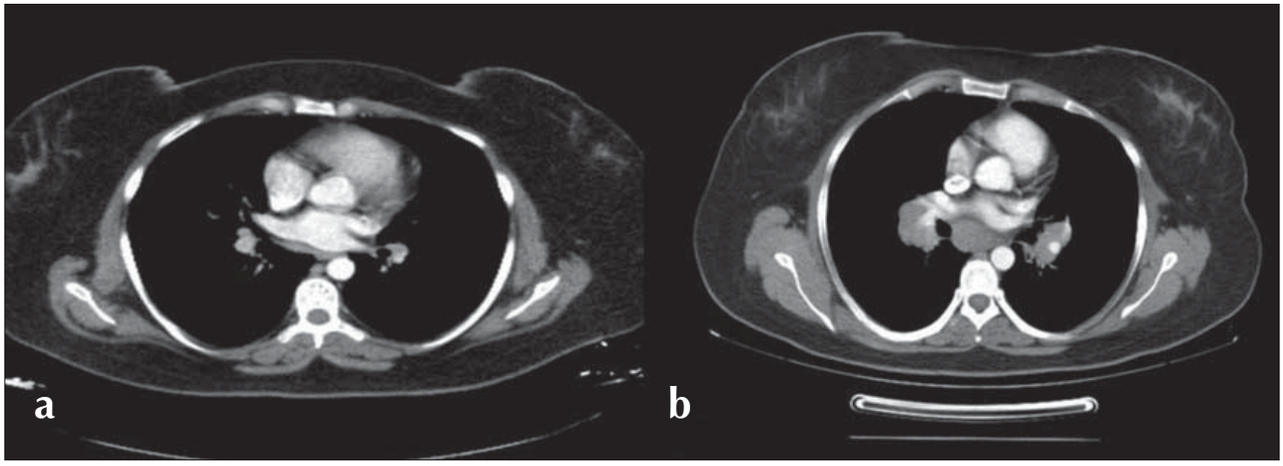

Figure 2. a, b. Axial view of thorax CT of the patient: (a) before treatment of CS and (b) after treatment of CS.
CS: Cushing syndrome.

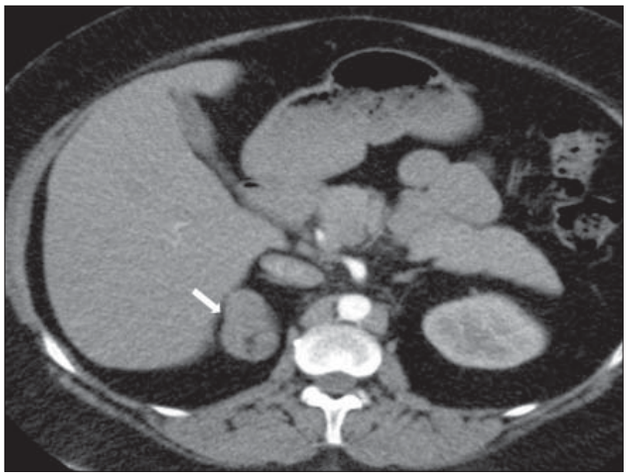

Figure 3. Axial view of adrenal CT of the patient. The arrow shows a 5 cm right adrenal mass.
CT: computed tomography.

reflects immune reactivation. We reported a case of sarcoidosis diagnosed after the remission of CS that may support this hypothesis.

The standard mortality ratio in patients with persistent moderate hypercortisolism due to untreated CS is increased 3.8-5.0-fold compared with that in the general population [6]. However, after successful normalization of cortisol levels, the mortality rate was similar to age matched population [6]. In a recent study, CS mortality was mainly attributed to cardiovascular causes and infection/sepsis in 50% and 21.4% of the cases, respectively [7]. The increased rate of infection mostly results from immunosuppression. The glucocorticoids affect lymphocyte proliferation through the inhibition of IL-1 and IL-2 production [8]. They also influence IL-10 secreting regulatory T cells [9]. Therefore, endogenous hypercortisolism contributes to immunosuppression in patients with CS.

Sarcoidosis is characterized by noncaseating granulomas and has been shown to be associated with other autoimmune disorders. The number of T cells in the granulomatous process are increased in this disease. Lungs are the most frequently involved organ in sarcoidosis. The identification of disease involvement can generally be determined by pulmonary function testing and chest imaging. Pulmonary function tests demonstrate decreased volumes and DLCO [4]. Bilateral hilar and symmetric and non-compressive lymphadenopathies are characteristic features and are often associated with right paratracheal and aortic-pulmonary window lymph node involvement in chest X-ray and thorax CT.

The patient was diagnosed with stage I sarcoidosis based on the presence of the noncaseous granulomas in the histopathologic evaluation of the fine needle aspiration and the supporting evidences such as radiologic findings, lymphocytic alveolitis, and increased serum ACE level and CD4/CD8 ratio.

After treatment of CS, rebound immunity occurs, particularly in patients with overt disease [2]. In rare cases, the treatment of CS may result in unmasking or aggravation of diseases responsive to glucocorticoid medication, such as thyroid, rheumatologic, and allergic diseases [2-10]. Sarcoidosis after remission of CS has been reported in few cases in the literature. Most of these patients were represented and diagnosed with cutaneus manifestations; however, our patient only had lung involvement [10]. The disease in our patient became symptomatic just after the corticosteroid replacement treatment decreased to lower levels. Therefore, high doses of glucocorticoids administered after remission of CS until restoration of pituitary adrenal axis may still be enough to suppress rebound immunity. This would be an explanation why the onset of symptoms was observed after a longer latency period in some cases.

In conclusion, excessive hypercortisolism may suppress the active inflammatory stage of sarcoidosis. However, the disease would become apparent after the reduction of cortisol levels following the treatment of CS.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

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CASE REPORT

Spontaneous Mediastinal Emphysema Associated with the Use of Synthetic Cannabinoid (Bonsai)

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Abstract

Spontaneous Mediastinal Emphysema (SME), which is a rarely seen case is defined as the detection of free air in the mediastinum without any trauma. Although rare, some cases secondary to drug use have been reported. In this study, two SME cases that developed due to the use of a synthetic cannabinoid known as "bonzai", which has recently become widespread in Turkey, are presented. We would like to emphasize that SME should also be considered in the differential diagnosis of patients who present with the symptoms of chest pain and dyspnea and have a history of drug use.

KEY WORDS: Mediastinal emphysema, drug use, synthetic cannabinoid

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INTRODUCTION

Spontaneous Mediastinal Emphysema, (SME) is defined as the presence of nontraumatic free air in the mediastinum. Spontaneous mediastinal emphysema may rarely develop secondary to drug use [1].

Patients frequently come to the emergency unit with complaints of dyspnea, chest pain, and findings of neck swelling, and respiratory insufficiency [1].

The drug known as bonsai, the use of which has become widespread among the youth in Turkey, is a synthetic cannabinoid [2]. We came across two cases in our clinic in the 2- month period between August and September 2014, possibly as an indication of a "bonsai epidemic".

CASE PRESENTATION

Both patients were admitted to the emergency unit with dyspnea and chest pain. In addition, there was hemoptysis in one of the patients. Moreover, they had complaint of cough for a few days. The ages of the patients were 19 and 30 years and both were male. They were hospitalized after obtaining their written and verbal informed consents. In their histories, it was learned that they used bonsai a few times in the last week, and they had not used any other drugs apart from bonsai.

On physical examination of the patients, subcutaneous emphysema was observed and crepitus was felt in the neck region. The chest radiographs of both patients were normal, their ECG's revealed normal sinus rhythm and D-dimer values were within normal limits. SME was diagnosed by thoracic computed tomography (CT) , after which a thoracic surgeon was consulted, and a decision to treat the patients without surgical intervention was made (Figure 1-4). The patients received nasal oxygen (2 l/min) and bronchodilator support.

The patients had normal vital findings, arterial blood gases, and chest radiographs. They underwent bronchoscopy to investigate possible endobronchial pathologies; however; both bronchoscopies revealed no endobronchial involvement. The patients showed full recovery and were discharged following 7 days of conservative treatment. They were referred to the Alcohol and Substance Addiction Treatment and Research Center (AMATEM) for treatment of addiction and they are still under follow-up as outpatients.

DISCUSSION

SME is the detection of free air in the mediastinum without a history of trauma. It has been reported that SME develops as a result of severe cough (i.e. a cough during an asthma attack), after overexertion or Valsalva maneuver. Air leaks through "visceral space", the trachea, the esophagus, or major vessels in the neck surrounding mediastinal structures, and passes through the diaphragm and joins the retroperitoneal space. Air can reach up to the mediastinum because

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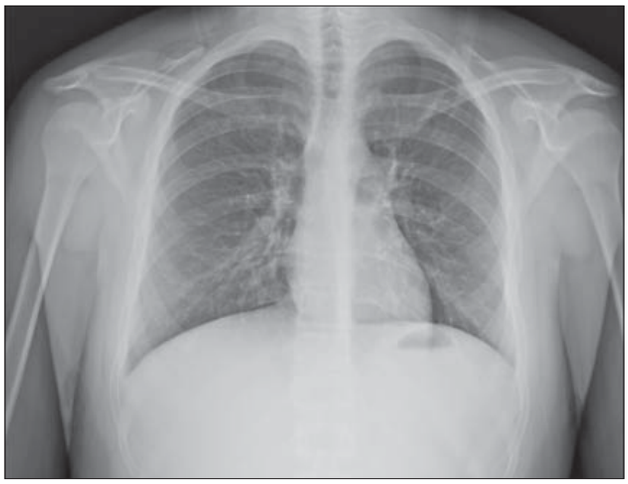

Figure 1. PA chest X-ray: Case 1.

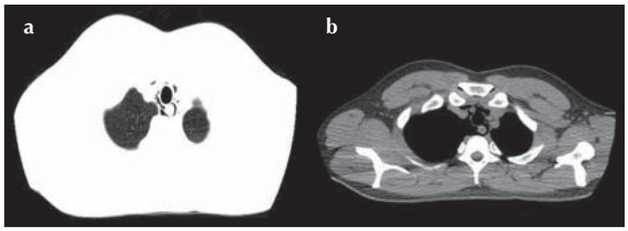

Figure 2. a, b Mediastinal emphysema and subcutaneous emphysema in thoracic CT of case 1.

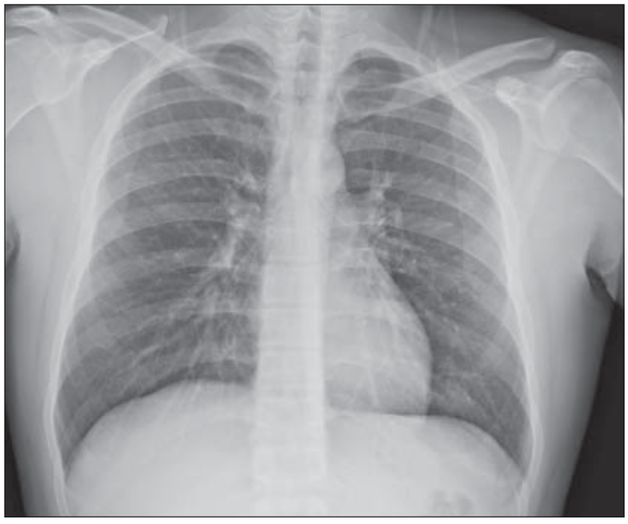

Figure 3. PA chest X-ray: Case 2.

of pathologies such as alveolar rupture and infection-related gas formation, with loss of structural unity, and it causes mediastinal emphysema. SME might develop among drug users due to overexertion. Drug use-related SME is known as a rare condition [1]. Drugs reported to date include ecstasy (3,4-methylenedioxy-methamphetamine and cocaine [3,4].

Drug use is rapidly becoming more widespread in Turkey as well as globally [2]. Drug users mostly present with the symptoms of neurological or cardiovascular systems; less frequently seen are dyspnea, hemoptysis, and chest pain [1].

Cases with diffuse infiltrates, nodular formations, or icy glass appearance in the lungs due to the use of bonsai and similar

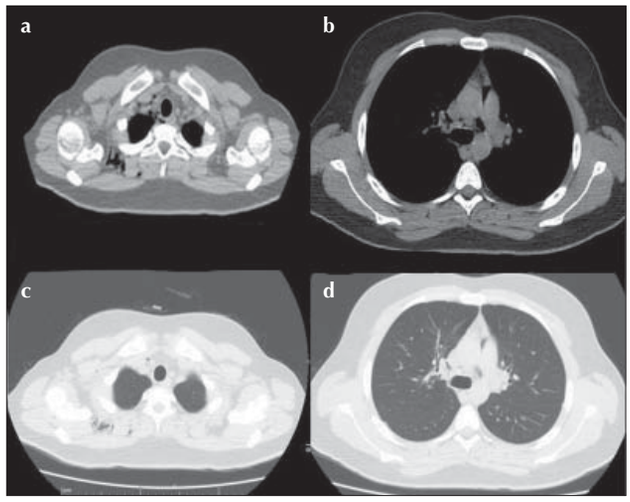

Figure 4. a-d. Mediastinal emphysema and subcutaneous emphysema in thoracic CT of case 2.

synthetic cannabinoids have begun to appear in the medical literature [5]. SME with subcutaneous emphysema has also been reported [1].

In SME, chest pain and dyspnea are prominent, though cough and hemoptysis may also be seen. Subcutaneous emphysema is often detected [1]. Generally, SME follows a benign course , but in the presence of predisposing factors, such as asthma, or if massive, it can lead to respiratory failure or may even be fatal [5]. It is frequently seen in young men [5,6].

On physical examination, auscultation reveals normal findings. In the presence of subcutaneous emphysema, crepitus is felt with palpation around the neck region [1]. Subcutaneous emphysema may not be detected in chest radiography. However, in the lower paratracheal and paracardiac areas, radiolucent areas can be detected [1]. In patients with a history of drug use, even if chest X-rays are normal, the presence of chest pain and dyspnea necessitates thoracic CT to rule out possible SME. On thoracic CT, air is observed in the mediastinum and subcutaneous region [1].

SME can usually be treated conservatively, but may also result in acute respiratory failure and sudden death. Monitoring patients in an intensive care unit can reduce mortality and morbidity [5,6]. The pathological findings and pathophysiology of the disease have not yet been completely determined because of the low number of cases with reported autopsy findings.

The differential diagnosis of SME includes diseases with high mortality, such as myocardial infarction, pulmonary embolism, tracheal and bronchial rupture, endobronchial tuberculosis, past radiation therapy, bronchoesophageal fistula, and particularly esophageal perforation [1]. After ruling out pulmonary embolism and acute myocardial infarction, bronchoscopy should be performed in order to eliminate possible endobronchial pathologies [7]. Moreover, gastroscopy/endoscopy may also be needed [7].

Medical treatment consists of supplemental oxygen, bronchodilators, and antibiotics, if necessary [1,5,6]. Decisions

regarding mediastinotomy for decompression should be made together with a thoracic surgeon [8].

In young male patients presenting with chest pain, dyspnea and hemoptysis, especially with a history or a suspicion of drug abuse,mediastinal emphysema should also be considered in the differential diagnosis.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

Peer-review: Externally peer-reviewed.

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

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