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Review

Original Investigations

Case Report

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Turkish Thoracic Journal is the conceptually scientific, open access and official publication of the Turkish Thoracic Society. The publication language is both Turkish and English and it is an international journal based on independent, unbiased, and double-blind peer-review principles.

Turkish Thoracic Journal started its publication life following the mergence of two seperate journals which are published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2007. Archives of both journals were passed on to the Turkish Thoracic Journal.

The aim of Turkish Thoracic Journal is to publish pulmonary disease-related clinical, experimental and epidemiologic studies that are scientifically highly qualified. Additionally, reviews, editorials, letters to the editor, and case reports are also accepted. Reports presented in meetings organized by the Turkish Thoracic Society Head Office or national and international consensus reports are published as supplements. The journal is published 4 times annually, in January, April, July and October. The target-groups are chest diseases physicians, thoracic surgeons, internal medicine doctors and practitioners interested in pulmonary diseases.

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2. The aim of the journal is to convey scientific developments in thoracic diseases and surgery, and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address thoracic diseases and cell biology, epidemiology, immunology, pathophysiology, thoracic imaging, pediatric chest diseases, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, puzzling cases, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

Presentations and reports of meetings organized by Turkish Thoracic Society Head Office and its branches can be published as supplements.

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

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

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Unpublished Resources (In Press)
Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. In press 1997.

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Smith J. New agents for cancer chemotherapy. Presented at the Third Annual Meeting of the American Cancer Society, 13 June 1983, New York.

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

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

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

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

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

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CONTENTS

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REVIEW

Pulmonary Mucormycosis Over 130 Years: A Case Report and Literature Review

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Abstract

Mucor is a ubiquitous fungus that belongs to the family of Zygomycetes, though a noninvasive saprophyte in the normal host, it can cause life threatening infections in immunocompromised patients, including angioinvasive pulmonary mucormycosis; a disease notorious for its high mortality. This article tracks the ever-changing management of pulmonary mucormycosis over the last 130 years, and how this affected mortality.

KEYWORDS: Pulmonary mucormycosis, posaconazole, fungal infection

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INTRODUCTION

Pulmonary mucormycosis is a rare but serious fungal infection that usually occurs in the presence of a defective immune system. Pulmonary mucormycosis was first described in 1876 by Furbringer [1]. Since then only a few hundred cases have been reported.

In a classic review in 1955, Baker [2] thoroughly described all mucormycosis cases previously reported; it included six cases in the old German literature and 10 cases in the American literature. He considered mucormycosis to be a new disease in the USA and attributed its increasing incidence to the amplified use of antibiotics, cortisone, and Adrenocorticotropic hormone ACTH. The respiratory tract was recognized to be the portal of entry for mucorales, and these fungi can easily invade arteries, veins, and lymphatics and produce thrombosis and infarction. In the first half of the twentieth century, no antifungal therapy was available except for potassium iodide. In 1971, Baker [3] further expanded his review to include 49 cases of mucormycosis (including 39 pulmonary cases), which were reported in the literature till that time.

The review by Tedder et al.[4] in 1994 included 30 patients who were treated at their institution and 225 cases reported in the literature; some of their patients had disseminated mucormycosis. Of the 92 patients diagnosed antemortem, 61% underwent medical treatment with antifungal agents, 21% were surgically treated, and 18% underwent combined medical and surgical therapy.

Francis et al.[5] described 87 cases of pulmonary mucormycosis reported in the literature from 1970 to 2000 after introducing flexible bronchoscopy. In his review, 55 patients underwent antifungal therapy, in which most received amphotericin B and only seven received an Azole. The overall survival rate was 44% and was higher in patients who underwent combined medical and surgical therapy.

In this study, we describe a patient with diabetic ketosis who presented subacutely with semi-invasive pulmonary mucormycosis infection and review 22 other cases of pulmonary mucormycosis treated with posaconazole reported in the literature since 2001 [6-22].

CASE PRESENTATION

A 21-year-old male patient was referred to our hospital for elective bronchoscopy because of 4-month history of recurrent respiratory symptoms and persistent pulmonary infiltrates that failed to improve even after different antibiotic courses. His symptoms included purulent yellowish sputum on coughing, occasional streaks of blood, feverish sensation, non-specific chest pain, anorexia, and weight loss of 18 kg in 4 months.

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Socially, he was a nonsmoker, worked at a gas station, and slept in a poorly ventilated work place.

Past medical history was significant for poorly controlled diabetes mellitus (DM) type 1 of 6-year duration (recurrent DKA and ketosis; HA1c, 11%).

On examination, vital signs were normal; patient was well looking, had decreased vesicular breathing sounds over both lung bases, and normal cardiovascular and abdominal examination. Laboratory test results revealed diabetic ketosis. CXR showed bilateral lower lobe infiltrates (Figure1). He was admitted to ICU, and IV insulin and fluid infusions were initiated.

In light of recurrent respiratory symptoms that failed to improve, pulmonary vasculitis was suspected; chest CT was performed (Figure2) that revealed consolidations in LLL (mainly L9) and RLL (mainly R6). Bronchoscopy showed spiral-shaped whitish gelatinous-like friable material that obstructed the orifice of the whole LLL (Figures 3 and 4). The bronchoscopist attempted to remove maximum material, restoring the patency of the left lower lobe bronchus; endobronchial and transbronchial biopsies were obtained, which revealed irregular non-septate hyphae branching at wide angles, which were typical for mucormycosis (Figure 5). The patient received dual antifungal therapy with amphotericin B and posaconazole for 2 weeks, followed by oral administration of posaconazole 400mg bid alone for another 6 months. He was followed up regularly in the out patient settings, where he continued to have residual symptoms. Repeat chest CT showed resolution of infiltrates in RLL, but significant progression of the disease in LLL. He eventually required wedge resection of L9,10 (Figure 6).

Review of the Literature

Methods: We searched PubMed for all pulmonary mucormycosis cases treated with posaconazole in the English literature and included only cases with pulmonary or Pulmonary or Pulmonary-plus disease. Twenty-three cases (including our patient) were identified in 18 articles published in 2000-2016.

Demographics and Underlying Conditions

Fourteen patients were males and seven were females, with a male-female ratio of 2:1; the gender was not mentioned for two cases. The mean age was 41.8 (range, 10-63) years.

Fourteen patients had hematological malignancy as their underlying condition and comprised maximum patients (60.8%), followed by six patients (26%) with organ transplantation and three (13%) with uncontrolled DM. Two patients (8.7%) had HIV, one (4.34%) had lupus nephritis, one (4.34%) had methimazole-induced neutropenia, and one (4.34%) had no known underlying condition (Note: A patient may have more than one underlying disease).

Imaging and Diagnosis

Table 1 (Radiographic manifestations of pulmonary mucormycosis and their distribution) outlines the radiographic manifestations of pulmonary mucormycosis. Most patients (26%) had infiltrates, cavity or nodules (17.39% each), consolidation (13%), and tracheitis (4.35%). In addition, in 30% of patients, radiographic manifestations were not mentioned.

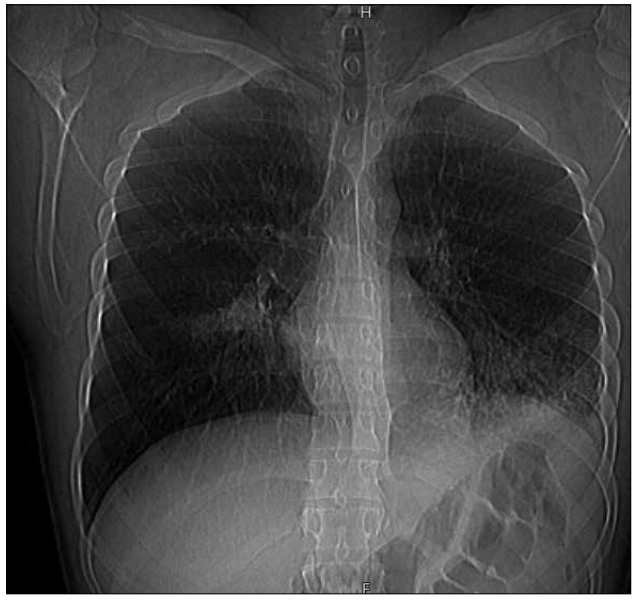

Figure 1. Chest xray showing bileteral lower lobe infiltrates

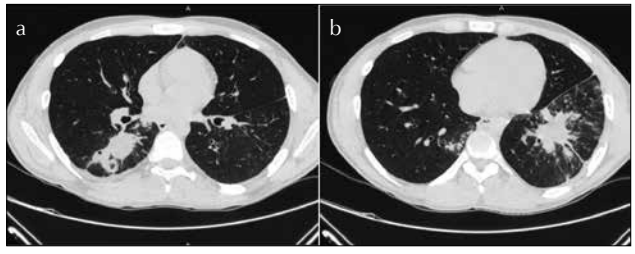

Figure 2. a, b. Chest CT showing consolidations in RLL and LL

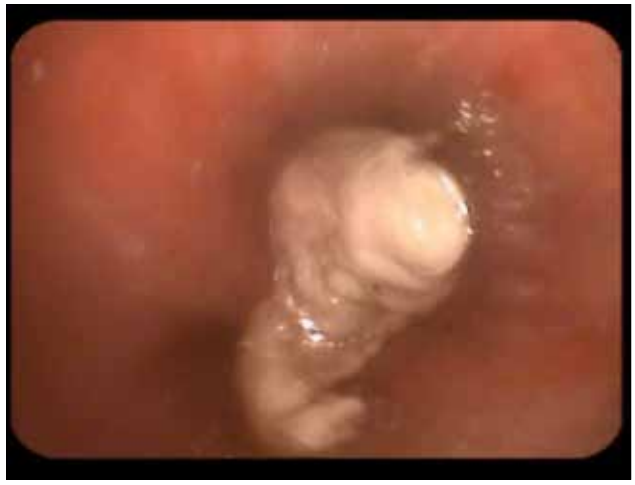

Figure 3. Bronchscopic view showing spiral-shaped whitish gelatinous-like friable material obstructing the orifice of LLL

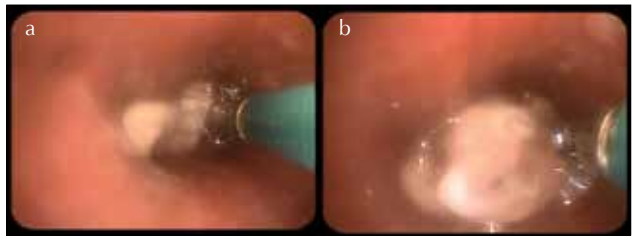

Figure 4. a, b. Bronchscopic view showing spiral-shaped whitish gelatinous-like friable material obstructing the orifice of LLL

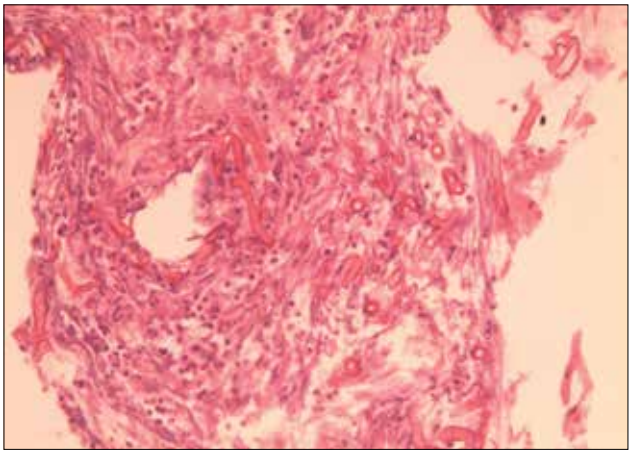

Figure 5. Histology showing irregular non-septate hyphae branching at wide angles typical for mucormycosis

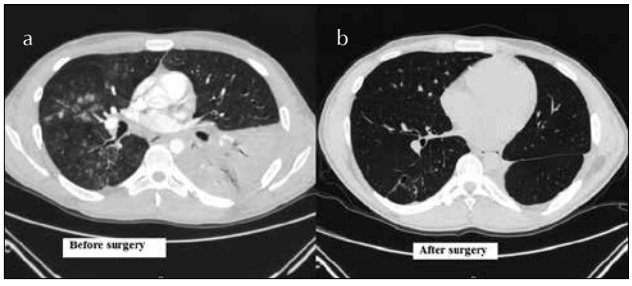

Figure 6. a, b. Cosolidation of LLL (Right image), Post wedge resection of L9,10 (Left image)

The distribution of the disease was as follows: 30% of patients had bilateral disease, 26% had upper lobes disease (including 4% RML), 8% had lower lobes disease, 4% had unilateral multilobular, and 30% distribution was not mentioned. In addition, one patient had tracheal ulcers.

The diagnosis was established using histology alone in most patients (83%), microbiology alone in 4% of patients, and both histology and microbiology in 13% of patients.

Therapy and Outcome

Of the 23 patients, 12 developed infection while undergoing prophylactic antifungal therapy (10 patients with malignancy and two with organ transplantation). Most patients (70%) underwent medical therapy alone, 30% underwent combined medical and surgical therapies, and none underwent surgical therapy alone.

All 23 patients received oral posaconazole therapy as part of their medical regimen. Posaconazole doses ranged from 600 to 800 mg/day in divided doses, and the therapy duration ranged from 2 weeks (because of patient death) up to 7 months. Oral posaconazole has poor bioavailability; however, if administered with a high-fat meal, the bioavailability increases by 400%. In one patient, administering the drug with high-fat meals and the use of 2 mg loperamide twice daily (for chemotherapy-related diarrhea) increased the posaconazole level from 262 to 708 ng/mL [20].

Other antifungals used were IV liposomal amphotericin B in 82% of patients and an echinocandin in 8.7% of patients. Table 2: (Therapy and outcomes). Liposomal amphotericin B was administered IV at a dose of 5-10 mg/kg for a duration that ranged from 1 week to 3 months. The primary reason for discontinuation was the development or fear of acute kidney injury. One patient also received amphotericin B deoxycholate by aerosol up to 5.1 g of accumulated doses, in addition to four sessions of endobronchial instillations of amphotericin B deoxycholate (20 mg in 10 mL normal saline in 5-mL aliquotes) through the working channel of the bronchoscope [8]. Surgical treatments were performed if the antifungal therapies were believed to be inadequate in controlling the disease; they mainly comprised local debridement with wedge resection or lobectomy.

The overall survival was 52.1% (12 patients survived); a large gap in survival rates was noted between medical therapy alone group (survival, 31.2%) and combined medical and surgical therapy group (survival, 100%). The distribution of survival according to the underlying disease is shown in Table 3 (Survival according to underlying disease). The lowest survival rate at 42.85% was noted among patients with malignancy.

Table 1. Radiographic manifestations of pulmonary mucormycosis and their distribution

Distribution of disease	Number of pts	%
RUL	2	9
RML	1	4.25
RLL	1	4.25
LUL	3	13
LLL	1	4.25
Bileteral	7	30.5
Unilateral Multilobular	1	4.25
Not mentioned	7	30.5
Total	**23**	100
Pulmonary Features	**Number of pts**	**%**
Inflitrate	6	26.09
Cavity	4	17.39
Consolidation	3	13.04
Nodules	4	17.39
Tracheitis	1	4.35
Not mentioned	7	30.43
Total	**23**	100.00

Table 2. Therapy and outcomes

Therapy	Number of pts (%)	Survival (%)
Medical+ Surgical	7 (30%)	7 (100)
Medical alone	16 (70%)	5 (31.2)
Total	**23 pts**	**12 (52.1)**
Antifungals used		
Amph	19 (82.6)	9 (47.3)
Posaconazole	23 (100)	12 (52.1)
Echinocandin	2 (8.7)	1 (50)

Table 3. Survival according to underlying disease

	Underlying disease and survival rates	
Underlying Disease*	**Patient No.(%)**	**Patients survved No.(%)**
DM	3 (13)	3 (100)
Malignancy	14 (60.8)	6 (42.85)
HIV	2 (8.7)	1 (50)
Organ Transplantation	6 (26)	3 (50)
Others	2 (8.7)	1 (50)
None	1 (4.34)	1 (100)

*A patient may have more than one underlying condition

Table 4. Comparison between four literature reviews

		This Review	Lee et al. [4]	Tedder et al. [5]	Baker [3]
	Number of patients	23	87	255**	39***
	Mean Age	41.8	44	41	44
	M:F ratio	2 to 1	3 to 1	7 to 3	2.4 to 1
Underlying Disease*	DM	13%	56%	32%	23%
	Malignancy	61%	32%	83.50%	46%
	HIV	8.70%	0	0	0
	Organ Transplantation	26%	11.40%	8%	0
	Others	8.75	24%	23.50%	13%
	None	4%	12.60%	0	2%
Reported Survival		52.10%	44.00%	35.00%	10.00%

*A patient may have more than one underlying disease
**Including patients with disseminated mucormycosis
***Pulmonary mucormycosis cases only

In conclusion, pulmonary mucormycosis is a life-threatening condition caused by molds in the order of mucorales, they usually present as an angio-invasive disease. Though widely spread in nature -especially in soil and decay matter- they rarely cause human disease, luckily because our immune system is so effective at eliminating them. However with the increasing number of patients who receive immunosuppressive medications or organ transplantation more cases of pulmonary mucormycosis are expected to be seen. In all four mentioned reviews 2-12% of patients had no known underlying disease Table 4 (Comparison between four literature reviews). To our knowledge this is the first review of the use of Posaconazole in pulmonary mucormycosis infections. The survival rate appears to be increasing with the ever expanding armamentarium of antifungal therapy, it was 10% in Baker`s review, 35% in Tedder et al. [5] 44% in Lee et al.[4] and 52.1% in our review Table 4.

Our patient described here was mildly immune suppressed due to poorly controlled diabetes mellitus type 1, and recurrent ketosis, had been exposed to damp poorly ventilated work place. Surprisingly he was relatively clinically well despite the presence of semi-invasive pulmonary disease on lung pathology. This highlights the importance of considering mucormycosis in patients at risk even with mild immunosupression and subacute presentation [23].

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

Diffusely Increased Splenic Fluorodeoxyglucose Uptake in Lung Cancer Patients

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Abstract

OBJECTIVES: This study aimed to investigate the association of diffuse splenic F-18 fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT) with tumor maximum standardized uptake value (SUVmax), presence of distant metastases, and hematological and inflammatory parameters.

MATERIAL AND METHODS: Initial FDG PET/CT of 15 lung cancer patients with diffuse splenic FDG uptake were retrospectively analyzed (Group 1). Twelve patients who recently underwent FDG PET/CT for histopathologically proven lung cancer were enrolled as the control group (Group 2). All 27 patients had hematological data, including C-reactive protein (CRP) level, within 5 days before or after PET/CT. To determine SUVmax, the region of interests included the tumor, liver, spleen, and iliac crest. The possible associations between the spleen/liver (S/L) and bone marrow/liver (BM/L) ratios and tumor SUVmax, presence of metastasis, and hematological parameters were evaluated.

RESULTS: The S/L ratio and hemoglobin (Hb) levels were different between the two groups (p=0.000 and 0.05, respectively). The number of patients with anemia were significantly higher in Group 1 than in Group 2 (p=0.02). Although mean Hb levels were different between the two groups, there was no correlation between Hb levels and S/L ratios. There was no significant difference between the two groups with respect to the numbers of patients who had an accompanying infection site. Only CRP levels were correlated with S/L ratios in Group 1 among various other parameters (r=0.559, p=0.05).

CONCLUSION: Our results suggested that inflammation degree correlated with increased splenic FDG uptake in lung cancer patients and was enhanced by anemia. Systemic inflammation and anemia could be important causes of diffusely increased splenic FDG accumulation on PET/CT examinations of lung cancer patients.

KEYWORDS: Spleen, anemia, inflammation, lung cancer, fluorodeoxyglucose, positron emission tomography

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INTRODUCTION

In normal individuals, splenic F-18 fluorodeoxyglucose (FDG) uptakes are generally diffuse and less compared with hepatic FDG uptakes on positron emission tomography/computed tomography (PET/CT) and does not change with age or differ with sex [1]. Splenic uptake is always evaluated as a pathological finding, mainly representing a spleen neoplasm, splenic metastasis of other primary tumors, or an infection. Diffusely increased splenic FDG uptake on PET/CT is an incidental and rare finding, and its clinical implication remains unclear.

The spleen is the largest secondary lymphoid organ in our body and is responsible for initiating immune responses to antigens via deposited lymphocytes. Erythrocytes, granulocytes, and circulating mononuclear cells are also associated with the splenic cords. Extramedullary hematopoiesis is active in the red pulp during fetal life but can also be activated during chronic anemia [2]. The tumor weight stress was also suggested to be a cause of secondary (splenic) erythropoiesis, and we assumed cancer anemia to be a cause of increased splenic uptake. A few studies recently suggested that anemia, inflammations, and infections were associated with splenic FDG uptake in cancer patients on PET/CT [3-6]. Although anemia and infection are frequently observed in cancer patients, most patients do not show increased splenic FDG accumulation on PET/CT. This study aimed to investigate the association of diffuse splenic FDG uptake on PET/CT with tumor maximum standardized uptake value (SUVmax), presence of distant metastases, and hematological and inflammatory parameters to clarify the clinical significance of diffuse splenic uptake in lung cancer patients.

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MATERIAL AND METHODS

We retrospectively reviewed the FDG PET/CT examinations reported in our department between 2010 and 2015 and collected 145 reports that defined visually increased splenic uptake. After excluding most lymphoma patients and 11 patients with tumors other than lung cancer, 15 lung cancer patients (nine females and six males) with diffuse splenic FDG uptake on their initial scan, which also hematological data such as C-reactive protein (CRP) level in 5 days before or after PET/CT, were included as the patient group (Group 1; Figure 1). As the control group (Group 2), 12 randomly selected, histopathologically proven lung cancer patients (two females and 10 males), which also had hematological data such as CRP level in 5 days before or after PET/CT, were enrolled (Figure 2).

The laboratory data used for the evaluations included CRP level (mg/dL; normal range, 0-0.5 mg/dL) as the marker of active inflammation, white blood cell (WBC) ($x10^3$/uL; normal range, 4.0-11.0$x10^3$/uL), monocyte number (Mon) ($x10^3$/uL; normal range, 0.24-0.36$x10^3$/uL), neutrophil number (Neu) ($x10^3$/uL; normal range, 1.56-6.13$x10^3$/uL), lymphocyte number (Lym) ($x10^3$/uL; normal range, 1.18-3.74$x10^3$/uL), erythrocyte number (Erit) ($x10^6$/uL; normal range, 3.7-5.2$x10^6$/uL), hemoglobin (Hb) concentration (g/dL; normal range, 12.5-15.0 g/dL), and hematocrit (Htc) (%; normal range, 36.0%-46.0%).

FDG PET/CT Imaging Procedure

Positron emission tomography/computed tomography imaging was performed using a PET/CT equipment (G.E. Discovery STE) in our department. The patients were fasted for 4 h before PET/CT. Blood glucose levels of all patients were measured before the procedure using a glucometer (One Touch Select. China). Then, 296-555 MBq (8-15 mCi) FDG was injected via the antecubital vein of the patients when glucose levels were <180 mg/mL. Each patient was advised to remain idle for 60 min for accurate monitoring of the FDG bio-dispersion in the body. Following bladder drainage, the patients were supinely positioned on the PET/CT monitoring bed. Three-dimensional (3D) emission and transmission scanning with an average of 7-8 bed positions from the vertex to the thigh were completed in 30 min. Sequential cross-sections of 0.6-cm thickness were prepared, comprising the covered regions in axial, coronal, and sagittal planes.

SUV Measurement

For semi-quantitative evaluation, SUVmax normalized for body weight was calculated as follows: radioactivity in the region of interest (ROI; per ml)xlean body mass (kg)/injected radioactivity. ROIs were drawn including the majority of the organ of interest but within the borders (using the CT counterpart) at the same time. A spherical ROI: volume of interest (VOI) for 3D measurement was used for the liver, spleen, and bone marrow (BM). VOIs were manually placed on the tumor, liver, spleen, and iliac crest (for BM), to determine SUVmax. Liver SUVmax was calculated by allocating VOI with a volume of 20-50 cm^3 at the center of the right lobe. Spleen SUVmax was calculated by averaging the estimations of three 4-8 cm^3 elliptical VOIs, which were placed in different portions of the organ. BM SUVmax was determined by calculating the mean of the estimations of elliptical 2-5 cm^3 VOIs, which were allocated in both iliac crests. All ROI placements, so the measurements of SUVmax were performed by only one author, to avoid any possible effect of interobserver variability. Spleen/liver (S/L) and BM/liver (BM/L) ratios were calculated by dividing the spleen (S) and BM SUVmax by the liver SUVmax.

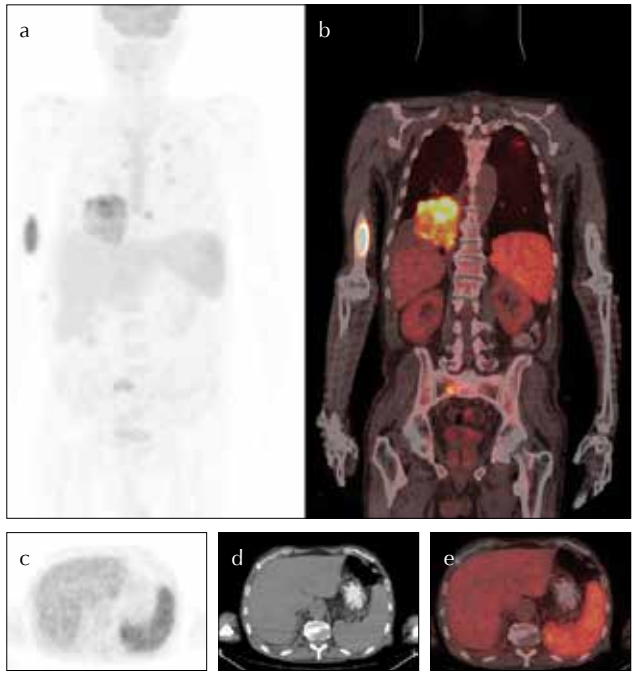

Figure 1. a-e. FDG PET/CT images of an 80-year-old patient with squamous cell carcinoma of the lung and accompanying pneumonia. The primary tumor in the lower lobe of the right lung and metastatic mediastinal lymph nodes, bone metastases were seen in the maximum intensity projection image (a). Coronal-fused FDG PET/CT (b), axial PET (c), CT (d), and axial-fused PET/CT (e) images show the diffuse splenic FDG uptake greater than the diffuse liver FDG uptake. The calculated SUVmax of the involving regions was as follows: TmSUVmax, 9.;, SSUVmax, 5; LSUVmax, 3; bmSUVmax: 2.8; S/L and BM/L ratios were 1.66 and 0.93, respectively. Laboratory findings were as follows: WBC, 5.5×10^3/uL; Neu, 4.3×10^3/uL; Hb, 9.5g/dL; Htc, 29%; Erit, 3.6×10^6/uL; and CRP, 12.9 mg/dL

Statistical Analysis

The differences between the two groups were analyzed to better understand the factors associated with the presence and absence of diffuse splenic uptake. Furthermore, the possible associations between S/L and BM/L ratios and tumor SUVmax, presence of metastasis, various hematological parameters were evaluated.

Mann-Whitney U test was used to compare continuous variables of the two groups, and T-test was used to evaluate the mean values of ages of two groups. The chi-square test was used to compare the two groups of categorical data. Spearman's rho correlation was used to determine the association between the parameters described above and diffuse splenic uptake, BM FDG uptake. A p value of ≤0.05 was defined to be statistically significant. Statistical evaluations were performed by Trakya University Medical Faculty Department of Biostatistics.

Exclusion Criteria

Patients with tumors other than lung cancer, those with a prediagnosis of lung cancer but without histopathological confirmation, lung cancer patients in follow-up who were previously treated, and those who did not have hematologi-

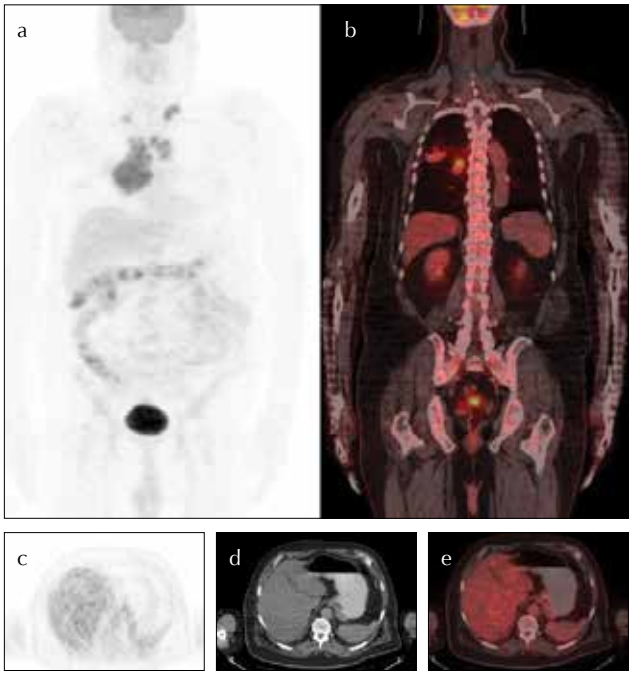

Figure 2. a-e. FDG PET/CT images of a 68-year-old patient with small cell lung cancer and accompanying pneumonia. The maximum intensity projection image (a) shows the primary 8-cm tumor in the hilum of the right lung and mediastinal, supraclavicular metastatic lymph nodes. The splenic FDG uptake was less than the hepatic FDG uptake, on coronal-fused FDG PET/CT (b), axial PET (c), CT (d), and axial fused PET/CT (e) images. The calculated SUVmax of the involving regions was as follows: TmSUVmax: 15.3, SSUVmax: 2.7, LSUVmax: 3.1, BMSUVmax: 3.5. S/L and BM/L were calculated as, 0.87, 1.1, respectively. Laboratory findings were as follows: WBC, 8.9×10^3/uL; Neu, 5.5×10^3/uL; Hb, 13.9g/dL; Htc, 41%; Erit, 4.6×10^6/uL; CRP, 3.03 mg/dL

cal data in 5 days with FDG PET/CT dates were excluded. Patients with liver cirrhosis, autoimmune disease, sarcoidosis, or hematopoietic diseases were also excluded.

Ethics

This retrospective study was approved by the Scientific Ethics Committee of Trakya University Medical Faculty.

RESULTS

Table 1 summarizes the characteristics of the patients in the two groups. Although the mean BM SUVmax and BM/L ratios of Group 1 were higher than those of Group 2; this difference was not statically significant. Liver SUVmax and tumor SUVmax were not different between the two groups. CRP levels of all patients in Groups 1 and 2 were higher than the normal range. Moreover, CRP levels of the two groups were not significantly different. Only SSUVmax, S/L ratios, and Hb levels of the two groups were significantly different (p=0.000 and 0.05, respectively).

Although all 27 patients had increased CRP levels, some did not have a proven site of infection in their records (Table 2). The number of patients who had an accompanying infection was not significantly different between the two groups. Presence of distant metastases did not significantly differ between the two groups. The number of patients with anemia were significantly higher in Group 1 than in Group 2 (p=0.02; Table 3).

Table 1. Patient characteristics and differences in parameters between the groups

	Group		
	1 (Patients; n=15)	**2 (Controls; n=12)**	**p***
Age (year)	66.07±12.139	70.58±9.298	0.29**
Hb (g/dL)	10.040±1.6326	11.467±2.0015	0.05*
Htc (%)	30.407±5.0089	34.567±6.3784	0.09
Erit ($\times10^6$/uL)	3.6420±.62923	3.9775±.61834	0.29
WBC ($\times10^3$/uL)	14.8400±21.16185	11.2100±7.46666	0.96
Lym ($\times10^3$/uL)	1.4813±1.53968	1.4958±.87843	0.42
Mon ($\times10^3$/uL	0.4973±.32756	0.6900±.31720	0.08
Neu ($\times10^3$/uL)	13.0173±21.22921	8.7683±7.07956	0.92
CRP (mg/dL)	9.6200±6.61490	7.2608±5.40268	0.30
Ssuv	3.553±.8895	2.358±.3450	0.000*
Lsuv	2.553±.7367	2.542±.5368	0.96
BMsuv	2.613±.7160	2.258±.8361	0.19
S/L	1.4233±.25559	0.9292±.10291	0.000*
BM/L	1.0580±.31992	.8733±.24077	0.11
tmsuv	11.533±8.6472	11.311±6.9452	0.54

Hb: hemoglobin; Htc: hematocrit; Erit: erythrocyte number; WBC: white blood cell; Lym: lymphocyte number; Mon: monocyte number; Neu: neutrophil number; CRP: C-reactive protein; Ssuv: spleen SUVmax; Lsuv: liver SUVmax; BMsuv: bone marrow SUVmax; S/L: spleen/liver ratio; BM/L: bone marrow/liver ratio; tmsuv: tumor SUVmax. * Mann-Whitney U test, ** T-test

Table 2. Diagnosis for accompanying infection/ inflammation

	Group 1 (n=15)	**Group 2 (n=12)**	**Diagnostic criteria**
No evidence of İnfection or Inflammation	6	6	No radiological and clinical evidence
Pneumonia	7	4	Fever, CT,±sputum culture
Mastoiditis		1	Cranial MR
Meningitis	1		Cerebrospinal liquid culture
Osteomyelitis	1		Microbiologic culture
Lymphadenitis		1	Microbiologic culture

CT: computed tomography; MR: magnetic resonance

Table 3. Number of patients with anemia, infection, and distant metastases in each group

	Group 1 (n=15)	**Group 2 (n=12)**	**p***
Anemia (n)	13	5	0.037*
Infection (n)	9	6	0.61
Distant metastases (n)	7	5	1.000

* chi-square test

Table 4. Comparison between four literature reviews

	S/L		BM/L	
Spearman's	**r**	**p**	**r**	**p**
tmsuv	–0.292	0.29	0.459	0.08
CRP	0.508	0.05*	0.140	0.61
Hb	0.072	0.80	–0.108	0.70
Htc	–0.020	0.94	–0.208	0.45
Erit	–0.143	0.61	–0.290	0.29
Mon	0.241	0.38	0.559	0.03*
Neu	0.011	0.97	0.581	0.02*
Lym	0.138	0.62	0.201	0.47
WBC	0.018	0.95	0.559	0.03*
Age	0.136	0.62	–0.124	0.66

tmsuv: tumor SUVmax; CRP: C-reactive protein; Hb: hemoglobin; Htc: hematocrit; Erit: erythrocyte number; WBC: white blood cell; Lym: lymphocyte number; Mon: monocyte number; Neu: neutrophil number; S/L: spleen/liver ratio; BM/L: bone marrow/liver ratio

The mean Hb levels were different between the two groups, but there was no correlation between the Hb levels and S/L ratios. CRP levels had a significant positive correlation with S/L ratios in only Group 1 among various parameters (r=0.508; p=0.05). BM/L ratios were positively correlated with WBC, Neu, and Mon in all 27 patients (r=0.559, p=0.03; r=0.581, p=0.02; and r=0.559, p=0.03, respectively). Table 4 shows the correlation coefficients and significances between S/L ratios of Group 1 and multiple parameters and correlation coefficients and significances between BM/L ratios of all 27 patients and multiple parameters. There were no significant correlations between S/L ratios of Group 2 and any of the parameters (data not shown; p>0.05).

DISCUSSION

The spleen, the largest secondary lymphoid organ, is associated with immune responses, as well as secondary hematopoiesis when needed. Extramedullary hematopoiesis is active, especially in the fetal life, but can also be activated during chronic anemic processes [2]. The impaired erythropoietin production in cancer patients who have anemia may be partly because of the production of inflammatory cytokines in response to the tumor [7,8]. Such cytokines also could distort the ability of BM to respond the circulating erythropoietin. Few studies have recently suggested that anemia, inflammatory cytokines, and refractory acute infections were associated with splenic FDG uptake on PET/CT in cancer patients [3-6]. Moreover, anemia and infection are frequently observed in cancer patients, and most patients do not show increased splenic FDG uptake on PET/CT. Because tumors were suggested to be the cause of stress, high cytokine levels, inflammation, and anemia, we investigated whether tumor SUVmax and tumor spread had an association with increased splenic uptake. Some tumor types have been reported to have a tendency to show increased splenic FDG uptake [4]. To avoid this kind of association and to homogenize patient population, we particularly investigated lung cancer patients. We also enrolled a control group, consisting of patients who underwent FDG PET/CT for staging of histopathologically proven lung cancer and who also had hematological data, within 5 days before or after PET/CT. Tumor SUVmax, presence of distant metastases, and hematological and inflammatory parameters were evaluated to clarify the difference between the two groups and clinical significance of diffuse splenic uptake in lung cancer patients. All the patients in both the groups had elevated CRP levels; the mean tumor SUVmax and tumor spread were not different between the two groups. Furthermore, there was no significant difference between the number of patients with known infection site in both the groups. In contrast to previous studies, we did not determine a direct significant correlation between Hb levels and S/L ratios [3]. Nevertheless, patients with anemia were higher in Group 1 than in Group 2 and had increased splenic uptake and decreased Hb levels. We may assume that patients with anemia have a tendency to show increased splenic uptake. This assumption is consistent with the spleen being a hematopoietic organ. However, only anemia itself did not appear to be the direct cause of increased splenic FDG uptake. The patients in both groups had high CRP levels but we determined that only CRP levels correlated with S/L ratios among various parameters in Group 1. This finding was in-line with that reported in previous studies of Nam et al.[3] and Pak et al.[4]. Activation and proliferation of macrophages is observed after the injection of granulocyte colony-stimulating factor (G-CSF) and this could be the reason of diffusely increased splenic uptake [9]. The tumor itself may secrete G-CSF and cause impaired erythropoietin production, anemia, and activation and proliferation of macrophages. Thus, the association between tumorigenesis, anemia, and inflammation is unique in an individual and is complicated.

Núñez et al.[10] reported that hematological parameters such as Hb, WBC, and platelet counts were correlated with the degree of splenic and BM FDG uptakes. We could not identify any association between BM FDG uptake and Hb levels or anemia. We determined that BM uptake reflects the number of circulating leucocytes in general. BM/L ratios were positively correlated with WBC and Neu in all 27 patients (r=0.559; p=0.03 and r=0.581; p=0.02, respectively). This finding was consistent with the previous reports that rendered diffuse BM uptake could be more likely because of the BM inflammatory changes; therefore the degree of BM FDG uptake correlates only with WBC, and the strongest correlation was determined with Neu [3,5]. This can be explained by the fact that BM FDG accumulation mainly reflects the total uptake by hematopoietic and vascular tissue. Because the neutrophil cell series is predominant in healthy BM hematopoietic cells [11].

Altogether, we determined a positive correlation between CRP levels and increased splenic uptake. The mean Hb levels were low in patients with increased splenic uptake. Although the mean CRP levels were not different between the two groups, we could not determine any association between CRP levels and splenic uptake of Group 2. Nevertheless, the degree of inflammation and anemia appear to be among the important causes of increased splenic FDG uptake on PET/CT in some lung cancer patients. Previous studies suggested that anemia, refractory infection site during PET/CT examinations, and possible systemic inflammations were the cause of diffusely increased splenic FDG uptake. However, in these

studies, either the direct results of the patient group were given or normal biochemical parameters and/or biochemical parameters of patients without cancer were used as reference. This study demonstrated that compared with a control group comprising lung cancer patients, it would be difficult to narrow the cause of diffusely increased splenic FDG uptake down to anemia and/or infection. This may be explained by the different immune responses of cancer patients among other things because we did not study different types of cytokines and the possible differences between predominating cytokine types and quantitative cytokine levels of the patients in the two groups. The difference between the duration and severity of anemia in the two groups may be another reason. As secondary information, we determined that BM FDG uptake could more likely reflect the inflammatory changes of BM. The degree of BM FDG uptake correlated only with WBC. The strongest correlation was determined between BM FDG uptake and the neutrophil cell series. We suggest that biochemical (hematological and inflammatory) test results of the patients should also be considered during PET/CT evaluations of cancer patients for correctly interpreting BM and splenic uptake.

Our study has some limitations because of its retrospective design. The patient population was small because the event was rare. Histopathological confirmations could not be obtained. Moreover, no follow-up data were available to make a prognostic assumption. Further well controlled prospective studies are needed to clearly determine the pathophysiological pathways and implications of diffusely increased splenic uptake and possible effect of it on prognosis during lung cancer surveillance.

Our results suggest that the degree of inflammation is correlated with an increased splenic FDG uptake in lung cancer patients, and it is enhanced by anemia rather than by an accompanying infection site. Systemic inflammation and anemia could be important causes of diffusely increased splenic FDG accumulation on PET/CT in lung cancer patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University School of Medicine.

Informed Consent: This study was a retrospective review of medical records, and requirement for informed consent was waived by our institutional review board.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

Frequency of Silent Brain Metastasis Before Prophylactic Cranial Irradiation in Small Cell Lung Cancer

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Abstract

OBJECTIVES: Prophylactic cranial irradiation (PCI) decreases incidence of brain metastasis and improves survival in patients with limited disease-small cell lung cancer (LD-SCLC) who achieved complete response (CR) after treatment. There is no satisfactory evidence about the necessity of new brain imaging for asymptomatic metastasis immediately prior to PCI. The present study aimed to evaluate the frequency of brain metastasis in SCLC patients without neurological symptoms who are candidates for PCI.

MATERIAL AND METHODS: The data files of 243 patients with SCLC referred for cranial irradiation were retrospectively reviewed. The patients with following characteristics were enrolled to the study; 1) LD-SCLC patients with CR after chemoradiotherapy who are candidates for PCI. 2) No neurological signs or symptoms of brain metastasis after chemoradiotherapy. 3) Having brain imaging at initial diagnosis and before PCI.

RESULTS: Ninety-nine patients (83 male, 83.3%) were included in this study. Median age was 60 years. Time interval between initial and reevaluation for brain metastasis was median 5.5 months (range; 4.7-7.1). Asymptomatic brain metastasis rate was 20.2% (18/99).

CONCLUSION: Even if local disease is under control, asymptomatic brain metastasis is not rare. Therefore, patients who are candidates for PCI after completion of chemoradiotherapy should be reimaged for brain metastasis before PCI.

KEYWORDS: Prophylaxis, brain, imaging, SCLC, metastasis

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INTRODUCTION

Approximately 30% of patients with small cell lung cancer (SCLC) initially staged as limited disease (LD) are candidates for combined model treatment (CMT) with curative intent. CMT with sequential or concurrent chemoradiotherapy (CRT) achieves complete response (CR) in 50%-60% of patients. However, the blood-brain barrier precludes the penetration of chemotherapeutic agents to the brain. The risk for brain metastasis occurrence is approximately 50% in the first 2 years after diagnosis [1]. Silent brain metastasis may develop at some point during the treatment course even in patients with a CR of intrathoracic disease. Emerging evidence suggests that prophylactic cranial irradiation (PCI) in patients with LD-SCLC who have achieved CR after CRT reduces the incidence of brain metastasis and improves survival [2,3]. However, the recommended dose for whole brain radiotherapy in patients with brain metastasis differs from the preferred dose for PCI [2].

Lung cancer guidelines recommend routine initial evaluations for brain metastasis with contrast-enhanced (CE) magnetic resonance imaging (MRI) or computed tomography (CT) in patients with SCLC [4,5]. The necessity of radiological reevaluation to detect asymptomatic brain metastasis before PCI has not been remarked on the guidelines, contrary to recommendations for the initial staging of SCLC.

Manapov et al. [6] detected silent brain metastasis in 32.5% of small patients size with LD-SCLC who were complete responders to CRT with pre-PCI second CE-MRI. However, there is a paucity of data on the frequency of asymptomatic brain metastasis in patients who are candidates for PCI. The present study aimed to evaluate the frequency of brain metastasis in SCLC patients without neurological symptoms who are candidates for PCI.

MATERIAL AND METHODS

Medical records of all consecutive patients with histologically proven SCLC, who were referred for palliative and prophylactic cranial irradiation to the Department of Radiation Oncology at the Chest Disease and Surgery Training and Research Hospital between January 2012 and December 2013, were retrospectively reviewed. Patients who were referred for PCI

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among these patients were extracted and further evaluated according to inclusion criteria. Patients who met the following inclusion criteria were included in the study: LD-SCLC patients who have achieved near CR or CR after CRT, patients without any neurological signs or symptoms of brain metastasis after CRT, patients who underwent CE brain imaging at initial diagnosis and before PCI.

In our hospital, standard work-up for initial staging in patients with lung cancer includes CE-CT of the chest/upper abdomen, bone scintigraphy, and CE-CT/MRI of the brain or CE-CT of the chest, PET/CT scans with [18F]-fluorodeoxyglucose, and CE-CT/MRI of the brain. CE-MRI is used as a problem solving tool for patients in whom CE-CT of the brain did not provide sufficient information for metastasis. Response evaluation (RECIST 1.1 criteria) is done with CE-CT of thorax/upper abdomen in 3-4 weeks after completion of the treatment and physical examination. Patients who are candidates for PCI are reevaluated with CE-CT and MRI of the brain and neurological symptom and signs.

The study was planned according to the World Medical Association Declaration of Helsinki (2013).

Statistical Analysis

Data were analyzed by using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA) statistical software.

RESULTS

Treatment data of 243 patients with SCLC who were referred for cranial irradiation to the Department of Radiation Oncology were reviewed. Ninety-nine patients (83 males, 83.3%) who met the inclusion criteria were included in this study. Median age was 60 years (44-81). Initial evaluation for brain metastasis was performed with CE-CT in 85.9% (85/99) and with CE-MRI in 14.1% of the patients (14/99). One patient with abnormal CT findings with suspected brain metastasis underwent further MRI testing. This patient was assessed in the MRI group. CRT was performed sequentially in 76% (75/99) and concurrently in 14% (14/99) of the patients. All patients received platinum-etoposide combination chemotherapy. Prior to PCI, reevaluation for brain metastasis was performed with CE-CT in 58.6% (58) and with CE-MRI in 41.4% (41) patients. We were skeptical of three cases included in the MRI group due to the cranial CT of these patients in terms of metastasis. Fourteen patients who had cranial MRI at initial staging were reevaluated with MRI. Median time interval between initial staging and reevaluation for brain metastasis was 5.5 months (range: 4.7-7.1).

Asymptomatic brain metastasis was detected in 20.2% (18/99) of the patients before PCI. In 50% (9/18) of them, metastasis was detected with MRI. Only 1 of 9 who had cranial MRI at reevaluation also had MRI at the first staging.

DISCUSSION

In our study, the frequency of asymptomatic brain metastasis was 20.2% in patients with CR after CRT and who were candidates for PCI.

Most chemotherapeutic agents cannot pass through the blood-brain barrier [7,8]. Because of that, the brain is considered the first site of recurrence in an aggressive tumor such as SCLC. Many randomized studies showed that in patients with LD-SCLC exhibiting CR after CRT, PCI reduces the incidence of brain metastasis and improves survival rate [2,9-12]. Timing of PCI is a matter of debate. There was a tendency toward a decrease in the incidence of brain metastasis with early PCI [2,12]. However, early PCI is not possible in all patients for various reasons. The likelihood of developing brain metastasis increases with the increased interval between the start of treatment and assessment of PCI. This interval is mostly more than 4 months in patients with SCLC [3]. Therefore, brain metastasis might develop during the combined treatment for SCLC. In our patient group, the median interval was 6.3 months. Manapov et al reported the time between SCLC diagnosis and second cranial imaging as 7 months (range: 4-10 months) [6].

Manapov et al. [6] detected silent brain metastasis in 32.5% (13/40) of LD-SCLC complete responders to CRT with pre-PCI second CE-MRI. In our study, we detected asymptomatic brain metastasis in 20.2% (18/99) of LD-SCLC patients with CR in the pre-PCI period. The lower frequency in our study population may be due to the shorter interval between SCLC diagnosis and the second cranial imaging.

There are several important limitations to our study mainly due to the retrospective study design. Different imaging methods were used at the initial staging and pre-PCI period in some patients. Owing to the low accessibility of cranial MRI in daily practice, half of our patients were evaluated with cranial CT at initial diagnosis. Guidelines recommend cranial CT or MRI at initial staging evaluation [4]. However, some studies show that cranial MRI is superior to CT in detecting silent brain metastasis [13].

Consequently, even if local disease is under control, asymptomatic brain metastasis is not rare. Therefore, patients who are candidates for PCI after completion of CRT should be reimaged for brain metastasis before PCI.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: This is a study analyzing of the patient data files. Because of that, patient informed consent was not obtained.

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ORIGINAL ARTICLE

The Effect of Working in a Smoke-Free Workplace on use of Smoking and Smokeless Tobacco

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Abstract

OBJECTIVES: The aim of this study was to evaluate whether smokeless tobacco (Maras powder) use increased among smokers working at smoke-free workplaces or not.

MATERIAL AND METHODS: In Kahramanmaraş city, 242 male workers who were current or former smokers, working at strictly smoke-free workplaces were included in this study. A total of 21 questions, including the Fagerstrom Test for Nicotine Dependence, were asked.

RESULTS: All the participants were male with a mean age of 29.33±6.66 years, and the age range was 17-55 years. Current smokers were 90 (37.2%) and former smokers were 152 (62.8%). Former smokers were asked the reason why they quit smoking; the predominant reasons were the health hazards of smoking and the financial burden of cigarettes. The quitting rate was significantly higher among married participants (p=0.023). Maras powder users were 184 (76%), users who never smoked were 54 (22.3%), and former users were 4 (1.7%). We asked the Maras powder users if they had been using it before the smoking bans, and 96 workers (51.1%) answered "no." The question "Did the use of Maras powder increase with smoking bans"? was asked, and 118 workers (62.8%) answered "yes." The level of education among Maras powder users was significantly lower than non-users (p=0.001).

CONCLUSION: Working in smoke-free workplaces is associated with increased rates of quitting smoking and also with increased use of Maras powder, a local form of oral smokeless tobacco.

KEYWORDS: Smoke-free workplace, Maras powder, smokeless tobacco

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INTRODUCTION

Tobacco is a plant that is considered to originate in the territory of North and South Americas [1]. The most common form of tobacco consumption in general is smoking, which is the most important cause of preventable deaths worldwide. According to the World Health Organization (WHO), each year worldwide, about 6 million people (9% of all deaths) die as a result of smoking-related diseases: in high-income countries, 18% of all deaths are associated with tobacco use; in medium-income countries, 11%; and in low-income countries, 4% [2].

Tobacco control has been undertaken with the support of international policies. WHO published the "Framework Convention on Tobacco Control (FCTC)" in 2003, which plays an important role in these regulations and is a directory guide for tobacco control in all countries [3]. This protocol agreement was approved by the Turkish Parliament and enforced in 2004. The WHO's MPOWER policy measures were published in 2008. In the same year, Turkey adapted the necessary law to combat smoking [4,5]. With this law, smoking in enclosed areas has been prohibited from 19 July 2009 and has been implemented in totality. In recent years, while smoking is decreasing in many developed countries, it is increasing in many low- and middle-income countries. This increase in tobacco use will cause an increase in deaths attributable to tobacco use in these countries [6,7].

There are many preparations for tobacco use that can be classified into two types: smoking tobacco and smokeless tobacco. Narghile is a type of non-cigarette smoking. In Turkey, 2.3% tobacco users use narghile [7]. Smokeless tobacco is absorbed by the nasal and oral mucosae. A form of smokeless tobacco called Maras powder (MP) is applied to the oral mucosa and is used mostly in the southeastern region of Turkey, especially in the cities of Kahramanmaraş and Gaziantep. It is obtained from a tobacco plant species known as Nicotiana rustica (Linn). Plasma nicotine concentrations of Maras powder users are 8-10 times higher than those of cigarette users [8,9].

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The purpose of this study is to determine whether the use of Maras powder, a form of smokeless tobacco, increases in workers strictly not allowed to smoke at workplaces.

MATERIAL AND METHODS

Out of 955 male workers working in a textile factory not allowed to smoke, 680 workers were queried; due to shift-work situation, 275 evening and night shift workers could not be evaluated. Out of these 680 workers, 268 workers did not want to contribute toward this study, either due to self-defining character as being a never-smoker or not willing to participate in this study. A total of 412 workers that were smokers and former smokers were included in the study and were requested to complete the questionnaire. We employed a 15-item questionnaire consisting of questions about smoking, alcohol consumption, Maras powder use, and education, and an additional 6-item Fagerstrom Test for Nicotine Dependence (FTND) questionnaire. When filling the questionnaire, the term "smoker" was used for workers who smoked regularly. The term "former smoker" was used for workers who smoked before [10]. In order to obtain correct results, personal identifying information was not taken within the questionnaire. Our study has been approved by the Ethics Committee of the Kahramanmaras Sutcu Imam University School of Medicine.

Statistical Analyses

The calculations were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 17.0 statistical software package. For statistical analysis, chi-square, independent t-test, and Mann-Whitney U test were used. Here $p<0.05$ was accepted as statistically significant.

RESULTS

Out of the 412 male workers participating in the study, only 242 (58.7%) could be evaluated. Workers not evaluated for the survey either had missing information or reported as being a never-smoker. The age range was from 17 to 55 years, and the average age was 29.33±6.66 years. Sociodemographic features of the workers are listed in Table 1. The smoking, drinking, alcohol consumption, and Maras powder use statuses are listed in Table 2.

Out of the 242 workers, 184 (76%) were using Maras powder (Table 2). The amount of daily Maras powder use was between one-half to two bags (each bag was approximately 20 g), the frequency range was 2-20 times per day, and mean frequency was 6.3±3.5 times.

When we compared the smoker and former smoker groups according to marital status, we found that married workers had higher rates of smoking cessation (p=0.023). Smoker and former smoker groups were compared according to Maras powder use, age, and education level, and the results are shown in Table 3.

We also found that Maras powder users had lower educational status and the difference was statistically significant (p=0.001). The mean age and marital status of Maras powder users and non-users are shown in Table 4.

Table 1. Sociodemographic characteristics of workers

Characteristics	Mean±SD	Min-Max
Age	29.3±6.7	17-55
Height	172.6±5.7	157-189
Weight	72.7±12.0	50-115
BMI	24.4±3.8	16.1-38.4
Marriage status	**n=242**	**%**
Married	200	82.6
Non-married	42	17.4
Education status	**n=242**	**%**
Uneducated	4	1.6
Primary school	79	32.6
Secondary school	71	29.3
High school	66	27.3
University	22	9.1

BMI: body mass index; Min: minimum; Max: maximum; SD: standard deviaiton

DISCUSSION

In the United States, at least 53000 annual non-smokers' deaths have been linked to passive smoking: for every 8 smokers, tobacco kills about 1 non-smoker. Since August 2001, smoking has begun to be prohibited in closed working environments by local regulations [11]. Turkey legalized the tobacco control law for a complete ban on smoking in all enclosed public areas and workplaces, and the WHO has stated this in its 2009 report [12]. In Turkey, the prevalence of tobacco use decreased from 31.2% in 2008 to 27.1% in 2012. Reduction was reported in both men (from 47.9% to 41.5%) and women (from 15.2% to 13.1%) [4]. The WHO reported that the adult smoking prevalence in Turkey was 22% in 2013 [13].

In a study from Turkey, persons being referred to an outpatient smoking cessation clinic were analyzed. Here, 83.7% of them were married, and the reasons for application to the clinic were asked: fear of deteriorating health was 44%; to be a good role model for their children and the desire to see their children's future, 16.3%; current illness, 9.8%; and shortness of breath, 6.9% [14]. In another study, an increase in cigarette prices was found to cause 2-3-fold more cessation or reduction of smoking in young and low-income people as compared to other reasons [15]. Our results were similar, and we found that smoking cessation was significantly higher among married than unmarried workers. The most common reason for quitting smoking was the harmful effect on health, followed by financial burden.

In a review about working in smoke-free workplaces covering 4 countries and 26 workplaces, Fichtenberg et al. [11] determined that 3.8% employees quit smoking and 3.1% reduced the number of cigarettes smoked. In the same study, it was shown that a 10% increase in cigarette prices led to a 4% decline in cigarette consumption in smoke-free workplaces. Smoking cessation in workplaces where a total smoking ban was applied was 2 times higher than places with a partial

Table 2. Status of drinking alcohol, smoking, and Maras powder use among workers

Habitudes of participants	n	%
Alcohol use (n=242)		
Yes	23	9.5
No	219	90.5
Smoking (n=242)		
Smoker	90	37.2
Former smoker	152	62.8
Cigarette type (n=157)		
Branded	112	71.3
Non-branded	35	22.3
Homemade	10	6.4
Reason of smoking cessation (n=152)		
Health hazards	101	66.5
Financial burden	43	28.3
Social pressure	4	2.6
Smoking ban	4	2.6
Maras powder use (n=242)		
Non-user	54	22.3
User	184	76.0
Former user	4	1.7
Maras powder use before smoking ban (n=188)		
User	92	48.9
Non-user	96	51.1
Use of Maras powder with smoking ban (n=188)		
Non-increased	70	37.2
Increased	118	62.8
Reasons of increased Maras powder use (n=131)		
Cost of cigarette	42	32.1
Smoking ban	41	31.3
Cigarette related complaints	48	36.6
Cigarette per day (n=81)		
<10 cigarette	59	72.8
11-20 cigarette	18	22.2
21-30 cigarette	1	1.2
>30 cigarette	3	3.7
Fagerstrom Nicotine Dependence Test (n=80)		
Low	41	51.3
Low-moderate	14	17.5
Moderate	8	10.0
High	11	13.7
Very high	6	7.5

BMI: body mass index; Min: minimum; Max: maximum; SD: standard deviaiton

Table 3. Comparisons of marital and educational status, mean age, and Maras powder use between smokers and former smokers

Characteristics	Smokers	Former smokers	p*
Marriage status			0.023
Married	69	133	
Non-married	21	19	
Mean age	28.9±6.9	29.6±6.5	0.38
Education status	4.2±1.0	4.0±1.0	0.09
Maras powder use			0.08
User	64	120	
Non-user	25	29	

*p<0.05 is statistically significant.

Table 4. Comparison of marital status, average age, and education between Maras powder users and non-users

Characteristics	Maras powder users	Maras powder non-users	p*
Marriage status			0.23
Married	160	40	
Single	24	14	
Divorced	0	0	
Average age	29.0	31.0	0.44
Education level**	4.0±1.0	4.5±1.1	0.001

*p<0.05 is statistically significant. **Uneducated: 1, Primary school: 2, Secondary school: 3, High school: 4, University: 5

smoking ban. The authors of the same study also emphasized that smoke-free workplaces not only protect non-smokers from the dangers of passive smoking but also encourage smokers to stop or decrease consumption [11]. In our study, we thought that the reasons for the high smoking cessation rate (62.8%) were related to the enforced total smoke-free workplaces, and that smoking was accepted as a cause for dismissal.

Smokeless tobacco is widely used in the USA. In the USA, 14% adult men are cigarette users and 6.5% are chewing tobacco, snuff, or dip users. The most commonly used tobacco product among US adults was cigarettes, followed by smokeless tobacco [13,16]. It was determined that smokeless tobacco increases the risk of oral, esophageal, and pancreatic cancers, and also increases the risk of stroke and heart attacks [17-20]. The American Heart Association does not recommend the use of smokeless tobacco as an alternative to quitting smoking or as a smoking cessation product [21]. However, in 2011, the American Council on Science and Health (ACSH) published a booklet entitled "Helping Smokers Quit: The Science Behind Tobacco Harm Reduction." In this booklet, it was shown that "smokeless tobacco use is at least 98% safer than smoking and it had a major effect on reduce smoking rates in Sweden, but it was not a gateway for smoking cessation" [22]. In our country, 94.8% smokers smoked manufactured cigarettes, and only 0.8% smoked water pipes [4]. There is no data on the prevalence of smokeless tobacco use in Turkey, but it is known to be used in southeastern cities. In these cities, studies discussing the side effects of Maras powder are very limited, and it is necessary to evalu-

ate the relationship of its use with diseases, especially cancer and heart diseases. It should be emphasized that American and Scandinavian smokeless tobacco products contain only tobacco, but Maras powder contains oak, walnut, or grape ash including tobacco, which may have an additional harmful effect [1].

In Sweden, men quitting smoking by using snus as a single support succeeded in stopping completely at a 66% rate, as compared to 47% of those using nicotine gum or 32% for those using nicotine patches; similar results were also seen in women. It was also emphasized that the use of snus in Sweden is related to a reduced risk of being a daily smoker and an increased possibility of quitting smoking [23]. Similar conclusions were also reached in Norway. The Norwegian Institute for Alcohol and Drug Research reported that the incidence of smoking in young Norwegian men had decreased from 50% in 1985 to 30% in 2007, while, at the same time, the use of snus increased from 10% to 30% [24]. In our study, we reported that in a full smoke-free workplace, the usage rate of Maras powder was 76%. After the smoking ban, the use of Maras powder increased in 62% participants. There is no prohibition on Maras powder use in the smoke-free workplace, which can increase the Maras powder use.

In our study, we found that among workers working in smoke-free workplaces, the rate of smoking cessation increased: with the smoking ban, the use of smokeless tobacco, namely, Maras powder, also increased. Additionally, we found that the use of these tobacco products was higher among people with low levels of education. We thought that with the expansion of the smoking ban, it is important to provide necessary education and support to prevent people from switching to smokeless tobacco.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kahramanmaraş Sütçü İmam University School of Medicine.

Informed Consent: We took permision from manager and volunteer workers were taken to study. The ethics committee was asked for permission from workers and was not needed because it was voluntary.

Peer-review: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE

Quality of Life Questionnaire for Turkish Patients with Primary Ciliary Dyskinesia

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Abstract

OBJECTIVES: Primary ciliary dyskinesia (PCD) is a major cause of progressive lung disease, and physiological measures do not reflect the impact of the disease on patients' daily symptoms or physical and social functions. We need valid and reliable health-related quality-of-life (HRQOL) measures in PCD to assess the symptoms and daily functions from the patient's perspective. Our aim was to develop a Turkish translation of PCD-specific HRQOL questionnairre to be used as outcomes in clinical trials.

MATERIAL AND METHODS: This study was conducted at the Division of Pediatric Pulmonology, Hacettepe University Faculty of Medicine and the Division of Pediatric Pulmonology, Marmara University Faculty of Medicine. Forward and back translations were performed by three different translators. We recruited participants with PCD from different age groups of both sexes, with an aim to represent a wide spectrum of disease severity and performed the prototype of the translation in these participants.

RESULTS: Five participants from each age group [children (6-12 years), teenagers (13-17 years), adults (18+ years) and parents of children aged from 6 to 12 years] responded to the HRQOL questionnaire. Content analysis of the questions included the following domains depending on age: Respiratory Symptoms, Physical Functioning, Emotional Functioning, Treatment Burden, Ears and Hearing, Sinus Symptoms, Social Functioning, Role Functioning, Vitality, Health Perceptions, School Functioning, Eating and Weight. After the participants have completed the questionnaire, a cognitive debriefing interview was conducted with them, and the results of the interviews were used to form a final version of PCD-specific HRQOL, ready for formal validation.

CONCLUSION: A Turkish translation of PCD-specific HRQOL questionnaire was developed to meet the standards set by international guidelines. This questionnaire is expected to be useful as end points in clinical trials for monitoring health outcomes and for improving clinical decisions.

KEYWORDS: Primary ciliary dyskinesia, quality of life questionnaire, forward translation

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INTRODUCTION

Primary ciliary dyskinesia (PCD) is a clinical disorder characterized by chronic lower and upper respiratory tract infections associated with impaired ciliary motility. It has clinical and genetic heterogeneity, and it is mostly inherited as an autosomal recessive disease. Its incidence has been reported to be 1 in 4,000-40,000 live births in various studies conducted to determine its frequency in different societies [1,2]. In our country, where the rate of consanguineous marriage is high, the incidence of PCD is also estimated to be high; however, its exact incidence is unknown. An abnormal ciliary structure and function are found in PCD. Recurrent pulmonary infections due to mucociliary clearance dysfunction in the respiratory system; lower and upper respiratory tract diseases such as bronchiectasis, sinusitis, rhinitis, and decreased hearing; infertility due to sperm immotility in men; and decreased fertility and ectopic pregnancy in women are observed. Situs inversus occurs in 30-50% of cases. On the other hand, hydrocephaly, ectopic pregnancies, and heterotaxia are less frequently seen [1-4].

While following PCD patients, parameters specific to the disease are used. Spirometry is an insensitive method for evaluating advanced lung damage. Although high-resolution computed tomography of the lungs is a useful technique in the monitoring of patients, it is impossible to perform tomography for all patients at certain intervals in practice [5-8]. Therefore, a quality of life scale is needed to evaluate the effects of PCD on patients [9].

At present, it is known that the quality of life scales, which are gradually gaining importance, are used as essential tools for assessing patients in clinical research studies as well as in the daily follow-up of chronic disease patients [9-11].

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In this study, the aim was to apply a pretest to PCD patients in various age groups and to the parents of PCD patients between the ages of 6 and 12 years to give the final form of the prototype scale of the quality of life scale for PCD patients (PCD-QOL scale, version 4.3) obtained after translating the English version into Turkish. It is suggested that the use of the Turkish version of these scales prepared for PCD will be beneficial in the follow-up of these patients and in clinical research to be performed on this disease with which an increasing number of people are diagnosed.

MATERIAL AND METHODS

This is a questionnaire study conducted by the Department of Pediatric Chest Diseases in the Faculty of Medicine at Hacettepe University and the Department of Pediatric Chest Diseases in the Faculty of Medicine at Marmara University. Ethical approval was received from the Non-interventional Clinical Research Ethics Board at Hacettepe University. Written informed consent was obtained from patients and their parents while completing the quality of life scale.

The study included children older than 6 years, adolescents and adults who were diagnosed with PCD, and the parents of PCD patients in the age group of 6-12 years. Those who did not complete the questionnaire were excluded. The diagnosis of PCD was established considering the patients' medical histories, clinical and radiological findings, and results of nasal nitric oxide measurements, electron microscopy, video microscopy, and genetic analysis.

In the study, with the permission of Dr. Jane Lucas from the group developing the scale and in accordance with the protocols prepared on this issue, the PCD-QOL scale (April 15, 2014, version 4.3) was first translated into Turkish by two researchers separately and the obtained form was re-translated into English by another researcher. The "prototype scale" was obtained by discussing every step with the developers of the scale on the phone [12].

In this study, the prototype scale was given the final form after being applied as a pretest to patients in different age groups and to the parents of children in the age group of 6-12 years. The plan was to apply it to larger groups including PCD patients and their parents for a validity-reliability study (Figure 1).

Statistical Analysis

For analyzing data, IBM SPSS (IBM Statistical Package for Social Sciences; Armonk, NY, USA) Windows 22.0 was used and descriptive statistical methods (mean, standard deviation, minimum, and maximum) were employed. Results were evaluated at the 95% confidence interval and significance at the level of $p<0.05$.

RESULTS

The patients were divided into groups including the parents of PCD patients, adult PCD patients, adolescent (age group of 13 and 18 years) PCD patients, and pediatric (age group if 6 and 12 years) PCD patients. The Turkish prototype of the scale was applied to five patients from each group in a quiet place in the outpatient clinic. The application of the prototype scale to individuals from each group (5 parents of PCD patients, 5 PCD patients in the age group of 6 and 12 years, 5 PCD patients of the age group of 13 and 18 years, and 5 adult PCD patients) and the cognitive review of responses with a one-to-one interview were performed in the Department of Pediatric Chest Diseases in the Faculty of Medicine at Hacettepe University. Patients of both sexes with different severities of the disease were preferred.

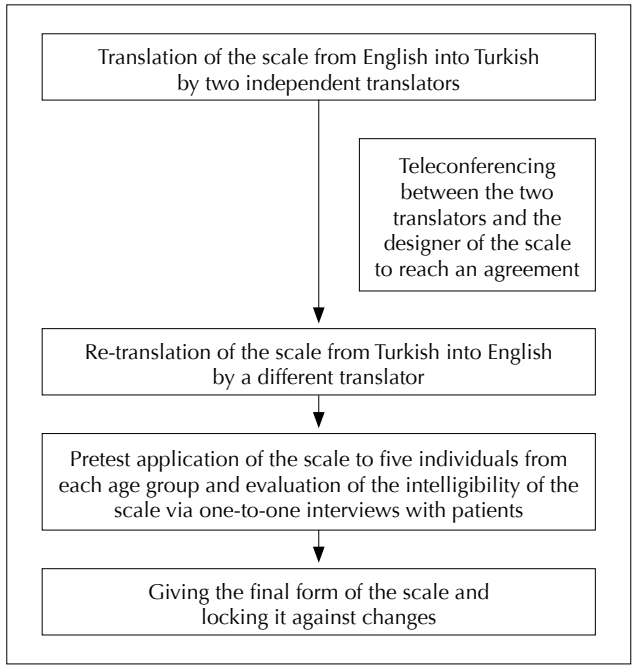

Figure 1. The algorithm of the procedures during the period in which the quality of life scale was given the final form

The following path was followed while applying the prototype scale (Figure 1). The prototype scale was completed by the patients by considering the instructions in the form. After completing the scale, a one-to-one interview was performed and the patients were asked to state what they understood from each question in their own words and what the question recalled at first reading. The patients were asked about the basis of their response to each question. They were asked how they found the questions, whether there were unclear words, and whether there were points that were important for PCD but overlooked. For an item or instruction with alternative words or explanations in the scale, the patients were questioned about which one would have been better. Moreover, the patients were asked about what they felt more comfortable with in their daily language. These views were recorded. In this way, the final form of the QOL-PCD scale that would be used in the actual validity study was obtained.

The quality of life scale included sub-groups involving different situations according to the different ages. These subgroups are shown in Table 1. The scale consisted of 37 items for the patients in the age group of 6-12 years, 41 items for the parents of the patients in the age group of 6-12 years, 43 items for the patients in the age group of 13-18 years, and 49 items for the patients in the age group of 18 years and above.

DISCUSSION

The aim of this study was to translate the English version of the PCD-QOL scale (version 4.3) into Turkish to follow the clinical course of the disease and to evaluate the effects of new treatments on patients. There are a few parameters that have been developed for this purpose in the follow-up of PCD patients.

Table 1. The sub-groups of the quality of life scale in different age groups

Measurement	Children in the age group of 6-12 years	Adolescents in the age group of 13-18 years	Parents of children in the age group of 6-12 years	Adults in the age group of 18 years and above
Evaluation of physical functions	X	X	X	X
Evaluation of emotions	X	X	X	X
Evaluation of treatment	X	X	X	X
Evaluation of ears and hearing	X	X	X	X
Evaluation of respiratory symptoms	X	X	X	X
Evaluation of sinus symptoms	X	X	X	X
Evaluation of social functions	X	X		X
Evaluation of social role		X		X
Evaluation of vitality		X	X	X
Evaluation of health perception			X	X
Evaluation of school functions			X	
Evaluation of nutritional status			X	

The quality of life scale has questions in the sub-groups including the evaluation of physical functions, emotions, treatment, hearing, respiratory symptoms, sinus symptoms, social functions, social role, vitality, health perception, school functions, and nutritional status, which were developed considering the different age groups.

In the quality of life scale for PCD, the aim was to evaluate the effect of respiratory symptoms on the daily life functions of patients by performing a cognitive evaluation with open-ended questions [12]. These questions are similar to those in other scales that are used for patients with cystic fibrosis and bronchiectasis, including respiratory symptoms such as chronic cough, shortness of breath, sputum will be better instead of phlegm, and headache, but the newly prepared quality of life scale also includes questions on symptoms specific to PCD patients such as nasal discharge, nasal obstruction, chronic otitis, and hearing problems [13-16]. The reason for adding these items is to question the symptoms developing in association with decreased mucus clearance from the lungs, nose, sinuses, and middle ear due to ciliary dysfunction [1-3,17].

Cystic fibrosis is a disease presenting with gastrointestinal symptoms and lower respiratory tract symptoms, and ear and hearing problems are rarely seen in this disease. Different from cystic fibrosis, symptoms related to the gastrointestinal system are rare in PCD patients. Despite the absence of pancreatic insufficiency findings in patients, a loss of appetite is observed during the periods of pulmonary exacerbation. These findings are mostly reported by parents. These kinds of questions were asked to the parents of children in the age group of 6-12 years [9].

There are differences in the quality of life scale according to ages. For younger ages, because symptoms for health perception and vitality evaluation are not dominant, there are no questions on these issues. However, it was observed that PCD affected vitality in adolescent patients. Another advantage of this scale is that it allows a comparison of the children's perception of symptoms with their parents' perception.

In a study by Dell et al. [9], it was specified that the development of the quality of life scale for PCD would be effective in the clinical course of the disease [9]. Lucas et al. [11] from England assessed the applicability of the quality of life scale in adult PCD patients, and it was decided that this test could be used after cognitive evaluations [18].

In conclusion, it is suggested that the quality of life scale for PCD patients can be commonly used in clinical studies and in the clinical follow-up of patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University School of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.U.Ö.; Design - N.E., H.U.Ö., B.K.; Supervision - H.U.Ö., B.K.; Resources -N.E., H.U.Ö.; Materials - N.E., H.U.Ö.; Data Collection and/or Processing - N.E., H.U.Ö.; Analysis and/or Interpretation - N.E., B.K., H.U.Ö.; Literature Search - N.E., H.U.Ö.; Writing Manuscript - N.E.; Critical Review - H.U.Ö., B.K.; Other - N.E., H.U.Ö., B.K.

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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.

NOTE: This questionnaire can be obtained from Professor Dr Uğur Özçelik and Dr Nagehan Emiralioğlu in Hacettepe University Faculty of Medicine Department of Pediatric Pulmonology and Professor Dr Bülent Karadağ in Marmara University Faculty of Medicine Department of Pediatric Pulmonology. This questionnaire can only be used and copy with the agreement and permission of the consortium of developers Prof Dr Jane Lucas, Sharon Dell, Margaret Leigh, Alexandra Quittner. After the validation of English version of this questionnaire Turkish validation will be performed.

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CASE REPORT

Mycobacterium Tuberculosis and Nontuberculous Mycobacteria Coinfection of the Lungs

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Abstract

Tuberculosis is highly prevalent in our country and nontuberculous mycobacteria (NTM) are frequently found in respiratory specimens recently. A 65-year-old woman was admitted with complaints of fever, cough, weight loss, and hemoptysis. On the patient's chest radiography an upper lobe cavity in both lungs and consolidation was detected. Acid-fast bacilli 4+ were observed in smear of sputum and culture results *M. intracellulare* and *M. tuberculosis* were observed together. The patient's treatment was arranged. Through this case, we want to emphasize that tuberculosis and nontuberculous mycobacterial disease can coexist.

KEYWORDS: *M. tuberculosis, M. intracellulare*, coinfection

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INTRODUCTION

Nontuberculous mycobacteria (NTM) pulmonary diseases are being increasingly detected. Cavitary NTM pulmonary disease is radiographically and clinically indistinguishable from pulmonary tuberculosis. Risk group of NTM infection include elderly persons; alcoholics; smokers with COPD**.**

CASE PRESENTATION

A 65-year-old woman was admitted with complaints of fever, cough, weight loss, and hemoptysis. We observed an upper lobe cavity in both lungs and consolidation on the patient's chest radiography and chest computed tomography scans (Figures 1 and 2). Tuberculin skin test result was 19 mm and acid-fast bacilli 4+ were observed in acid-fast bacilli smear of sputum. The patient was extremely cachectic and weighed only 28 kg. Drugs were set while considering the weight, and therapy with four drugs (INH, RIF, EMB, and PRZ) was started. COPD was a comorbid factor for tuberculosis, and HIV test was negative. Informed constent form was obtained from the patient. *Mycobacterium tuberculosis* was obtained from sputum cultures. In the follow-up culture results, *M. intracellulare* and *M. tuberculosis* were observed together. In order to verify the patient culture results, two sputum cultures taken on separate days were sent to another center, where the same results were obtained. INH and RIF susceptibility were detected in the culture tests. After *M. intracellulare* was observed in the two sputum cultures, clarithromycin treatment was also added to the first drugs. The patient regularly received the medication, and no side effects were observed. The patient came to to the outpatient clinic once a month in the follow-up period. In the third month of treatment, acid-fast bacilli smear of the sputum was negative. During subsequent follow-up, she did not give sputum sample. EMB and PRZ were discontinued in the third month; the remaining drugs were continued. During the sixth month of treatment, regression of the chest X-ray cavities and consolidation was observed, and the patient's weight increased to 35 kg (Figure 3). The patient did not come to the hospital and she died in the eight month of treatment. Through this case, we want to emphasize that tuberculosis and nontuberculous mycobacterial disease can coexist. Therefore, culture results should be carefully monitored.

DISCUSSION

Approximately 160 known species of *Nontuberculous mycobacteria (*NTM) that are commonly associated with lung disease in humans [1]. Historically, significant overlap between the symptoms of NTM pulmonary disease and tuberculosis has been described, probably because clinicians were looking for a disease resembling tuberculosis [2]. Nontuberculous mycobacteria (NTM) are frequently found in respiratory specimens from patients with *M. tuberculosis* pulmonary disease [3,4]. NTM have been frequently isolated from water soil, dust, and plants. They are quite resistant to water

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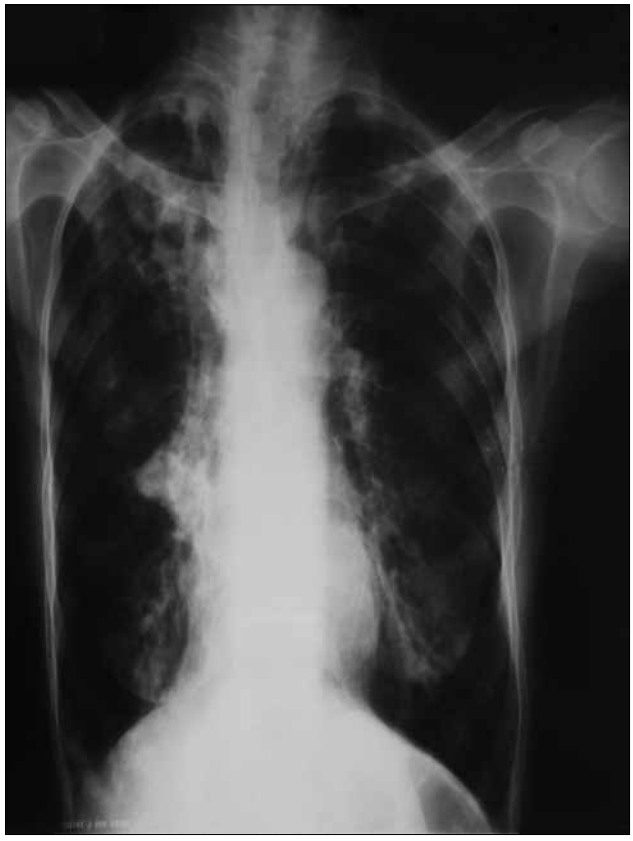

Figure 1. Patient's chest X-ray before treatment

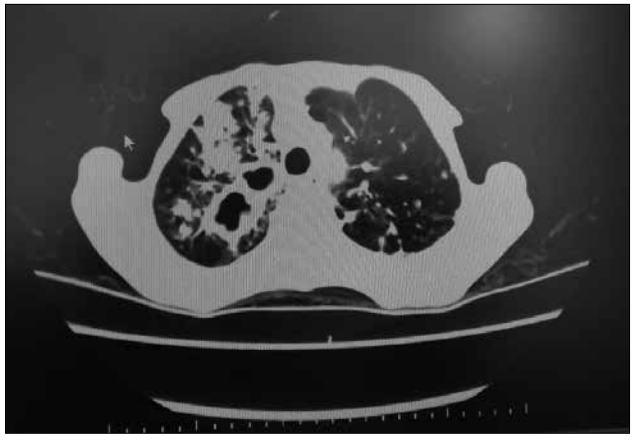

Figure 2. Patient's CT scan before treatment

disinfectants in common use, such as chlorine. Contact with contaminated environments may occasionally be responsible for infection in humans and animals, but the possibility of transmission from human to human is rare [5]. Risk group of NTM infection include elderly persons; alcoholics; smokers with COPD; and patients with chronic sinusitis, pulmonary fibrosis, gastroesophageal diseases, HIV, and a history of tuberculosis.

The lungs are easily affected by inhalation of aerosolized mycobacteria and is by far the most frequent site of human mycobacteriosis. In HIV() patients, the disease is indistinguishable from tuberculosis and is characterized by a very slow progression [6]. Cavitary NTM pulmonary disease is radiographically and clinically indistinguishable from pulmonary tuberculosis. Manifestations range from absence of

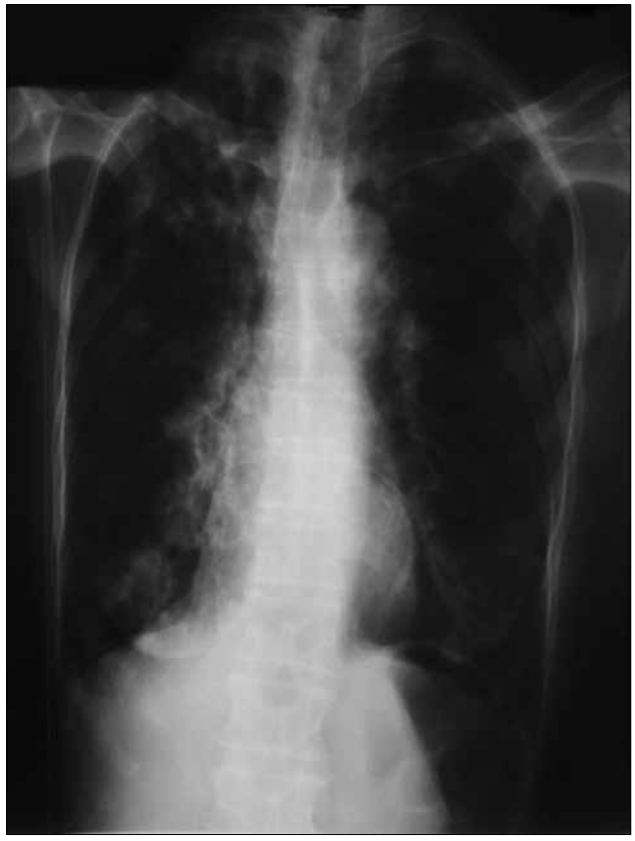

Figure 3. Patient's chest X-ray after 6th month treatment

symptoms to cavitary disease, and an X-ray may reveal fibrosis, upper lobe cavitation, nodular or parenchymal opacity, and pleural thickening. The most affected population is elderly patients with predisposing pulmonary conditions (such as silicosis, obstructive pulmonary disease, pneumoconiosis, previous tuberculosis, bronchiectasis, or cancer). Symptoms include cough, fever, weight loss, weakness, and respiratory insufficiency [7].

Interestingly, the increase in the proportion of pulmonary disease caused by NTM seems to be associated with a simultaneous decrease in the incidence of tuberculosis [8]. The guidelines of the American Thoracic Society provide strict criteria that are applicable in the presence of pneumopathy, for which any cause other than NTM has been excluded [9].

The most common types of NTM are *M. avium complex (M. avium* and *M. intracellulare), M. Kansasii*, and *M. abscessus*. Although species differentiation between *M. intracellulare* and *M. avium* in terms of clinical features and prognosis were not clearly defined. A recent large retrospective cohort study showed that patients with *M. intracellulare* pulmonary disease present more severe manifestations: lower body mass index, more frequent presence of respiratory symptoms and fibrocavitary disease, higher rate of smear-positive sputum, and worse prognosis, including more frequent initiation of antibiotic treatment during follow-up period and higher unfavourable treatment response than those in patients with *M. avium* pulmonary disease [10]. The same group also reported that patients with *M. intracellulare* pulmonary disease showed evidence of a more extensive disease on chest

computed tomography scan than did patients with *M. avium* pulmonary disease [11].

Cavitary NTM pulmonary disease is radiographically and clinically indistinguishable from pulmonary tuberculosis, which may lead to misdiagnosis in low-resource tuberculosis-endemic regions [12,13]. Patients with fibrocavitary disease usually require immediate treatment because cavitary disease is associated with a higher rate of mortality due to NTM pulmonary disease [14,15].

In some Asian countries where the mainstay of tuberculosis diagnosis is the acid-fast smear, there are concerns that a number of patients diagnosed with tuberculosis, especially with putative drug-resistant tuberculosis, might actually have NTM pulmonary disease (30.7% of isolates that tested resistant to isoniazid and rifampicin and 4% of tuberculosis retreatment cases in one study from China, similar to the African data previously mentioned) [16,17]. Some studies have shown that HIV(+) patients tend to have NTM and *M. tuberculosis* coinfection In publications made in this regard and in our country there is no case reviewed NTM and *Mycobacterium tuberculosis* are in same culture, also our patient was HIV (-).

Treatment of NTM pulmonary disease is difficult due to the uncertainty regarding when treatment should be started and which regimen is most likely to achieve successful treatment [18]. Initiation of NTM treatment should be individualized considering disease types, comorbid conditions, and age. Patients with fibrocavitary disease usually require immediate treatment because the presence of cavitary disease is associated with higher mortality rate [19,20]. A study demonstrated that clarithromycin and capreomycin have high antimicrobial activities against *M. intracellulare* isolates; clarithromycin and amikacin resistance could be more readily and rapidly detected using molecular scanning of corresponding drug target than conventional drug susceptibility testing.

In conclusion, tuberculosis is highly prevalent in our country. Recently, NTM pulmonary diseases are being increasingly detected. As in our case, tuberculosis and nontuberculous mycobacterial disease can coexist; therefore, culture results should be carefully monitored.

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

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