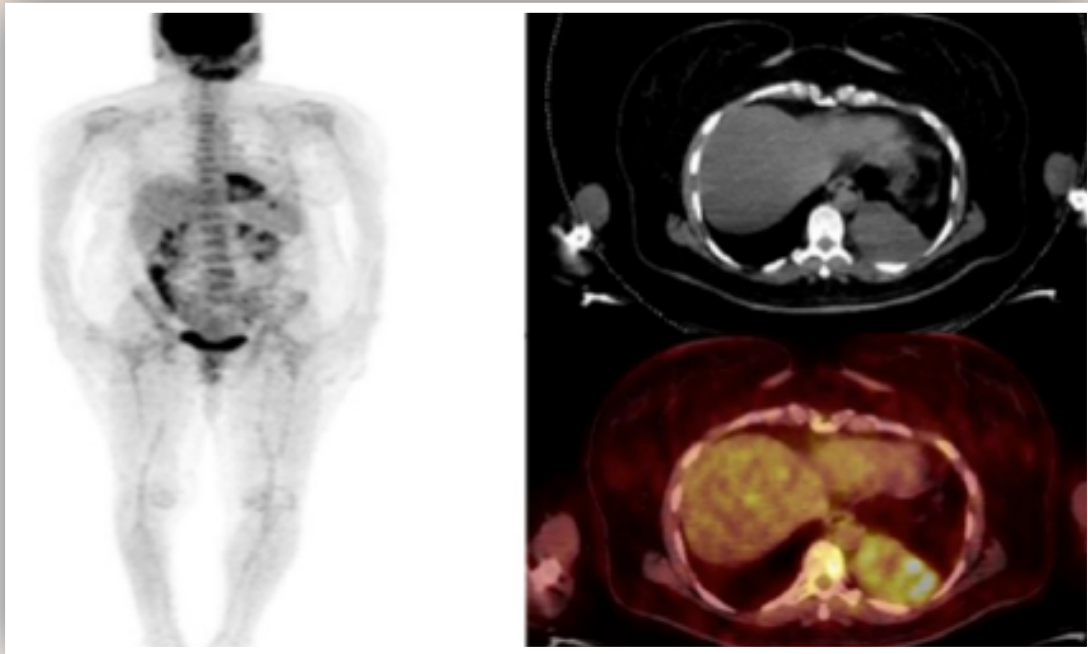


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Original Article

Routine practical contribution of innovations with 2015 World Health Organization Classification in the diagnosis of large cell lung carcinoma

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ABSTRACT

Background: Large-cell lung carcinoma (LCLC) is a relatively aggressive tumor and constitutes a small proportion of non-small-cell lung carcinoma (NSCLC). The purpose of this study was to investigate the clinicopathological characteristics of LCLC and reclassify patients according to the 2015 World Health Organization (WHO) criteria to improve the diagnosis rate of LCLC.

Materials and Methods: The clinicopathological data of 32 patients who were diagnosed as LCLC in our clinic between January 1999 and December 2016 and underwent surgery were retrospectively investigated. The 32 patients with LCLC accounted for 1.6% of the total 1935 patients who were diagnosed as having pulmonary cancer during the corresponding time period at our institution.

Results: There were 30 males and 2 females with a mean age of 56.4 (range, 39-76) years. The ratio of smoking / non-smoking patients was 22/32 (68.7%). Based on the new definition of LCLC, a total of 32 patients with LCLC were detected. 16 patients with null immunohistochemical features, 12 with no stains available, and 4 with unclear immunohistochemical features. Our 1, 3, and 5-year survival rates were 65.6%, 53.1%, and 46.9%, respectively.

Conclusions: According to the new classification, formerly diagnosed LCLCs were mostly reclassified as adenocarcinoma and non-keratinizing squamous cell carcinoma. LCLC, which became a more homogeneous group with the 2015 WHO classification, may significantly benefit from multimodal treatment with surgery.

Key Words: large-cell carcinoma, surgery, chemotherapy, radiotherapy

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Introduction

Large-cell carcinoma is a malignant tumor that was classified as two variants: large-cell neuroendocrine carcinoma (LCNEC) and basaloid carcinoma. LCNEC was described in 1991 by Travis et al. [1], and basaloid carcinoma was first described in 1992 [2]. Both variants were recognized as distinct clinicopathological entities with a dismal prognosis by the WHO classification in 1999 [3].

In the WHO Classification of 2015, there have been numerous important changes in terms of LCLC according to the 2004 WHO classification. LCLC is one of topics that has had the most specific and greatest changes from the 2015 WHO classification. For example, rare specific cell types: large cell neuroendocrine carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and rhabdoid tumor have been removed from the large cell carcinoma group and are no longer considered histologic subtypes [3-6]. In this study, the clinicopathological data from 32 patients with LCLC were retrospectively analyzed, with the aim of summarizing the specific clinicopathological features of LCLC, reclassifying the patients according to the 2015 WHO criteria, thereby improving the definite diagnosis rate of LCLC and showing the results of surgical resection as a treatment, and the postoperative follow-up.

Materials and Methods

The hospital records of 1935 consecutive patients with non-small-cell lung cancer (NSCLC) who underwent surgery between 1999 and 2016 were reviewed. The preoperative assessments included chest X-ray, and computed tomography (CT) of the chest and upper abdomen (Figures 1-3).

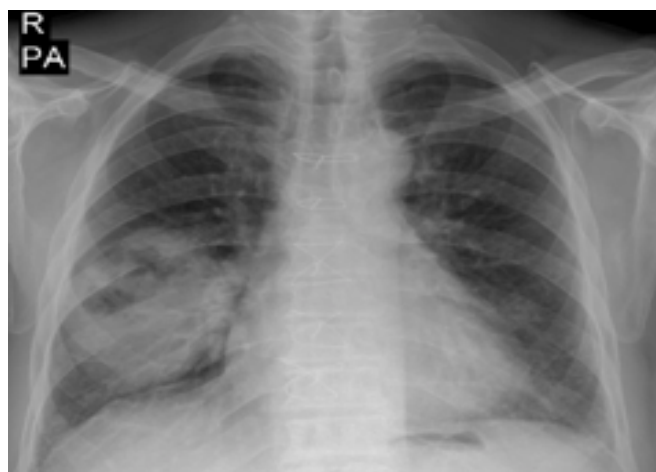


Figure 1. Chest X-ray of the thorax showed that the lung cavitation was about 9 cm in the right lower lung.



Figure 2. Computerized tomographic scan of the thorax, mediastinal window, showed that the lung cavitation was about 9 cm in the right lower lung.

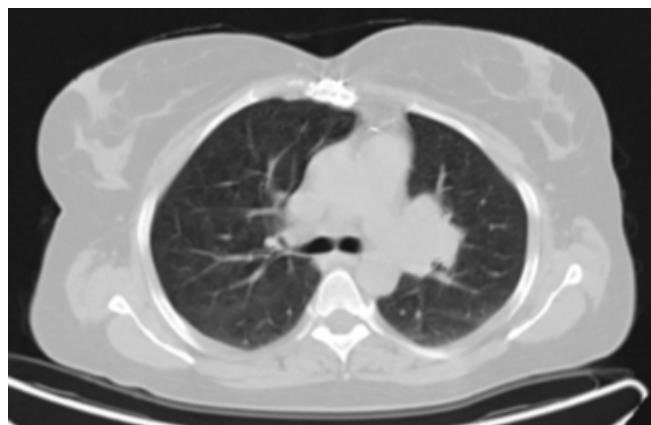


Figure 3. Computerized tomographic scan of the thorax, parenchymal window, showed that the lung mass was about 4 cm in the left central of the lung.

Clinical N2 status was defined by the presence of a lymph node more than 1 cm in a short axis diameter. Positron emission tomography (PET/CT) was routinely used after 2009 (Figure 4).

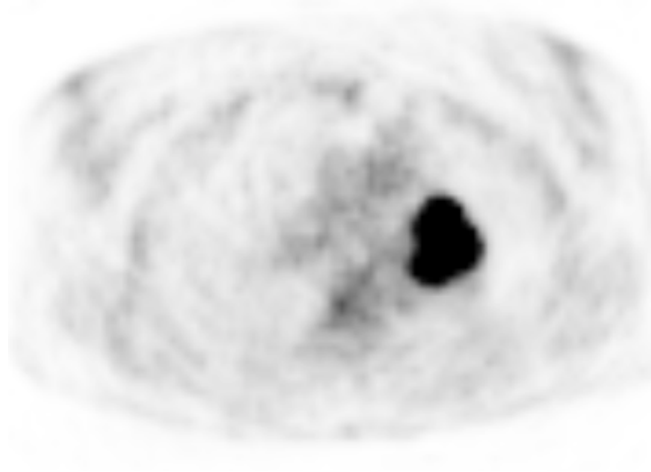


Figure 4. Positron emission tomography scan of the thorax, showed that the lung mass was about 4 cm in the left central of the lung.

Spirometry tests were routinely conducted in all patients and preoperative fiberoptic bronchoscopy (FOB) was also performed. Various types of thoracotomies were performed on these patients based on the location of the tumor and we planned pulmonary resection under single-lung anesthesia. We also performed either an anatomic or non-anatomic complete resection while preserving most of the functioning lung tissue. During the operation, undiagnosed tumors were confirmed using frozen section (FS) examinations. For centrally located lesions, FS examination of bronchial margins was performed routinely, with the hope of finding a tumor-free margin. In addition, systematic mediastinal and hilar lymph node sampling was conducted, and mediastinal lymph node dissection was performed if lymph node metastasis was confirmed by FS after sampling. All resected specimens, including the primary tumor and resected hilar and mediastinal lymph nodes, were examined to determine both the tumor histology and the extent of lymph node metastases. All tissues were sent for routine histopathologic examination after the surgery.

Adenocarcinoma, squamous cell carcinoma, and neuroendocrine differentiation were investigated in routine hematoxylin eosin (H&E) preparations of all cases. Immunohistochemical-studied cases were stained with P63, P40, Napsin A, and TTF1. Intracytoplasmic mucin was investigated using the mucin carmine technique. All specimens were reviewed by an experienced pathologist from our institution's department of pathology according to the revised histologic classification standards of lung cancer for the diagnosis and classification of LCLCs established by the WHO classification (4th edition).

The following parameters were investigated from the medical records: patient sex, age, smoking history, tumor size, tumor location, surgical procedure, pathologic TNM stage, adjuvant chemotherapy, time of recurrence, site of recurrence, response to treatment, and patient outcome. During the follow-up period, these data were prospectively recorded in the database, and then all patients were contacted either in person or by telephone. We performed routine follow-ups 4 times per year, checking symptoms and chest X-rays. We also performed chest CT at least once per year. If abnormal findings were observed, we used PET/CT to evaluate the hilar-mediastinal and extrathoracic lymph nodes, the lung field, and the abdomen.

The data were evaluated using the statistical package program IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA). The descriptive statistics were as follows: unit number (n), percent (%), mean $\pm$ standard deviation (SD), Median (Q1-Q3). The survival curve was calculated by the Kaplan–Meier method and compared using the Log-rank test for the univariate analysis. Categorical variables were compared by Pearson's Chi-square and Fisher's exact test. The differences were considered to be significant if the p value was less than 0.05. The normal distribution of the numerical variables was assessed using the Shapiro-Wilk normality test and Q-Q graphs.

Results

At our institution from January 1999 to December 2016, there were 32 LCLCs out of 1935 surgically resected primary lung cancers (1.6%). The mean age of the patients was 56.4 (range, 39-76) years; the male to female ratio was 30:2. Twenty-two patients (68.75%) had a history of smoking. The clinical symptoms were cough and expectoration (n = 10, 31.25%), bloody sputum or hemoptysis (n = 7, 21.87%), chest pain (n = 8, 25%), dyspnea and shortness of breath (n = 7, 21.87%), and fever (n = 3, 9.37%). Before the surgery, 32 patients underwent a sputum exfoliative cytopathology examination. A malignant tumor was confirmed in 5 patients (15.6%) in bronchoscopy, and in 15 patients (46.87%) in CT-guided transthoracic needle biopsy (TTNBx), and a definitive diagnosis was achieved in FS examinations in 11 (34.37%) patients, and postoperatively with mediastinoscopy in one patient.

In the CT findings, the maximum diameter of the tumors ranged between 2 and 20 cm, with an average of 4.8 cm. The majority of the tumors were peripherally located (81.25%, 26/32), only 18.75% (6/31) of tumors were centrally located. Twenty-one tumors were located in the right lung (11 superior lobe, 1 middle lobe, 5 lower lobe, 4 near the hilum of the lung) and 11 were located in the left lung (5 superior lobe, 2 lower lobe, 4 near the hilum of the lung). The imaging examination revealed lobulation in 18 cases (56.25%), cavitation in 5 cases (15.62%), atelectasis in 5 cases (15.62%), and mediastinal lymphadenopathy in 7 cases (21.87%). Routine immunohistochemical analysis was performed on 20 specimens.

All 32 patients (including one patient who underwent the mediastinal lymph node biopsy) were diagnosed as have LCLC (Figures 5,6). The tumors were classified as LCLC with unclear immunohistochemical features (12.5%, 4/32), with null immunohistochemical features (LCC-N) (50%, 16/32), and with no available staining (37.5%, 12/32). Left posterolateral thoracotomy was performed in 11 patients, and right posterolateral thoracotomy in 20 patients. Mediastinoscopy was performed in 7 patients and endobronchial ultrasound (EBUS) biopsy in 4. Thirty-one patients received surgical treatment including regional wedge excision (n = 1), lobectomy (n = 17), bilobectomy inferior (n = 3), lobectomy with chest wall resection (n = 2), and pneumonectomy (n = 8). No further surgical resection was applied in one patient because mediastinal lymph node metastasis (N2) was diagnosed with mediastinoscopy. The 7th Tumor, Node, Metastasis (TNM) classification of cancer tissues revealed 3 cases of stage IA, 6 cases of stage IB, one case of stage IIA, 13 cases of stage IIB, 8 cases of stage IIIA, and one case of stage IV. Among them, two patients received neoadjuvant chemotherapy, 17 patients received adjuvant chemotherapy, and 4 patients received postoperative radiotherapy. A total of 3 patients had palliative radiotherapy. One patient gave up chemoradiotherapy after confirmation of the LCLC diagnosis through biopsy of the lymph nodes. Among the 32 patients with LCLC, 21 were followed up for one year; however, 11 patients did not complete the follow-up period.

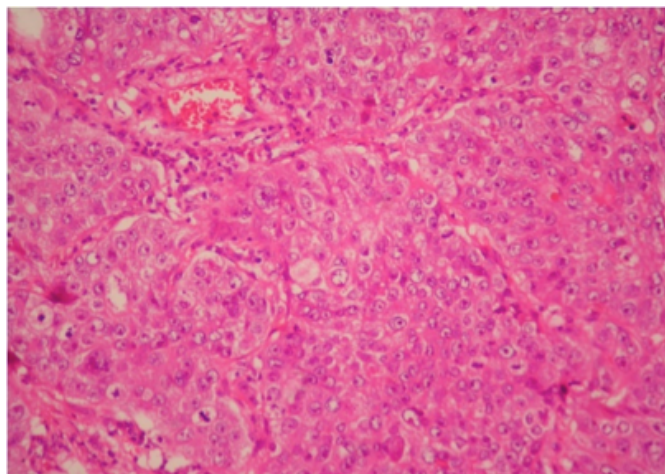


Figure 5. Large cell carcinoma consists of sheets of large polygonal cells (HEx200).

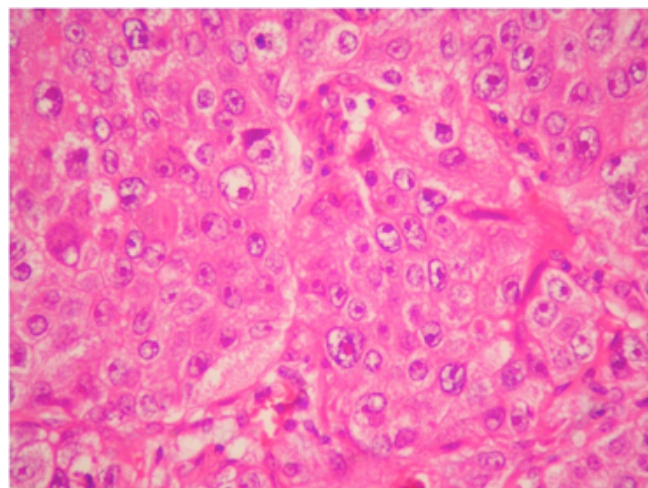
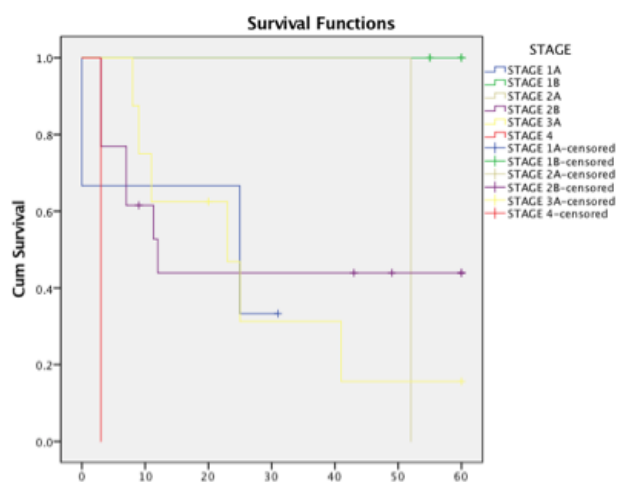


Figure 6. Large polygonal cells with vesicular nuclei, prominent nucleoli (HEx400).

The one-year survival rate of the patients was 65.6%. The three-year survival rate of the patients was 53.1%; 15 patients did not complete the follow-up period. The five-year survival rate of the patients was 46.9%; 17 patients did not complete the follow-up period. At the time of writing, the longest patient follow-up had reached the 125th month, and the patient is still alive. There have been 17 cases of mortality. As seen in our survival curve according to the stage of disease (Table 1 and Graph 1), our results showed the mean 1, 3 and 5-year survival rates were 88.2%, 76.5% and 64.7% in patients who received adjuvant chemotherapy, and 40%, 26.7%, and 26.7% in patients without adjuvant chemotherapy, respectively (Table 2 and Graph 2). Hereby 1, 3, and 5-year survival of patients with adjuvant chemotherapy better than patients without adjuvant chemotherapy ($p = 0.05$, $p = 0.03$, $p = 0.03$). There was no significant difference in survival in patients receiving adjuvant chemotherapy and radiotherapy together ($p = 0.594$). In addition, there was no significant difference in survival ($p = 0.773$) among patients who had neoadjuvant chemotherapy. Survival was longer in patients without metastasis ($p = 0.029$).

Table 1. Survival curve according to the stage.

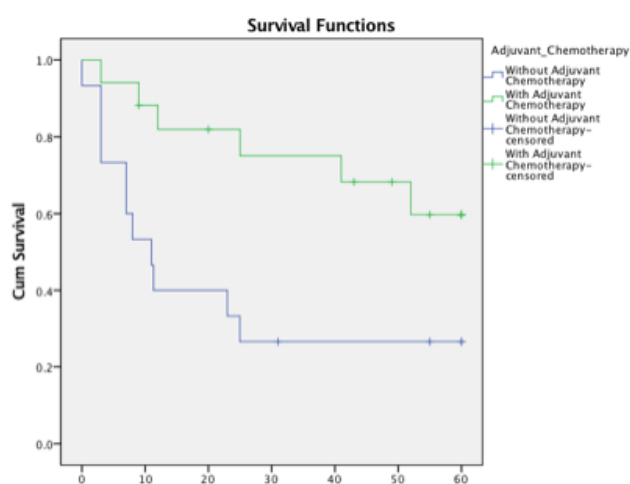
	Total number of patients	Number of patients died	Number of patients alive	%
Stage 1A	3	2	1	33.3%
Stage 1B	6	0	6	100.0%
Stage 2A	1	1	0	0.0%
Stage 2B	13	7	6	46.2%
Stage 3A	8	6	2	25.0%
Stage 4	1	1	0	0.0%
Overall	32	17	15	46.9%



Graph 1. Survival curve according to the stage.

Table 2. Comparison between patients who received adjuvant chemotherapy and without adjuvant chemotherapy.

Adjuvant chemotherapy	Total number of patients	Number of patients died	Number of patients alive	%
Without adjuvant chemotherapy	15	11	4	26.7%
Adjuvant chemotherapy	17	6	11	64.7%
Overall	32	17	15	46.9%



Graph 2. Comparison between patients who recieved adjuvant chemotherapy and without adjuvant chemotherapy.

Discussion

The 2015 WHO classification of lung tumors significantly alters the LCC category of the 2004 WHO classification. Many LCCs are now reassigned to either adenocarcinoma with solid pattern or non-keratinizing squamous cell carcinoma based on immunopositivity for adenocarcinoma markers or squamous cell carcinoma markers, respectively. NSCLC with negative immunomarkers that cannot be classified as adenocarcinoma with solid pattern (ADC-S) or non-keratinizing squamous cell carcinoma (NKSQCC) are now classified as LCC with null immunohistochemical features (LCC-N), a new WHO-defined category. The study group was reclassified according to WHO 2015 criteria [3-6]. LCCs with ambiguous immunostaining (LCC with unclear immunohistochemical features) or with no immunostaining available (LCC with no staining available) are also distinguished.

At our institution, 32 patients comprised 4 cases of LCLC with unclear immunohistochemical features, 16 cases of LCLC with null immunohistochemical features, and 12 cases of LCLC with no staining available. The other LCC subtypes from the 2004 WHO classification are reclassified as follows. Basaloid carcinoma has been moved to a subtype of squamous cell carcinoma. Lymphoepithelioma-like carcinoma has been moved to a group of “other and unclassified carcinomas.” Clear cell carcinoma and rhabdoid phenotype are now regarded as cytological features rather than a specific histologic subtype because these can occur in a variety of histologic types including adenocarcinoma or squamous cell carcinoma. LCNEC is now grouped with the other neuroendocrine tumors [4].

LCLC of the lung is a relatively uncommon and aggressive subset of NSCLC. More than 70% of patients have a history of smoking [7]. Therefore, smoking appears to be the primary cause in LCLC development. The mean age of patients ranges between 61.4 and 65 years [7,8]. Monica et al. found the male to female ratio as 33:9 in their study [8]. In our study, the ratio was 30:2, 93.75% of our patients were male. Twenty-two (68.75%) patients had a history of smoking and none of the female patients were smokers. As recognition and reporting of LCLC increases, the epidemiology of this neoplasm will be better defined, including possible associated environmental and genetic risk factors.

The true incidence of LCLC is low in all probability, although it has not been well defined. The incidence of LCLC through surgically resected patients appears to be between 3% and 9% based on the available literature [9,10]. Liang et al. presented a study of 174 cases of LCLC, which accounted for 5.7% of their total lung

The true incidence of LCLC is low in all probability, although it has not been well defined. The incidence of LCLC through surgically resected patients appears to be between 3% and 9% based on the available literature [9,10]. Liang et al. presented a study of 174 cases of LCLC, which accounted for 5.7% of their total lung

cancer cases. In the study, there were 80 cases of classic LCLC, 64 cases of LCNEC, six cases of combined LCNEC, 19 cases of basaloid carcinoma, three cases of clear cell carcinoma, and two cases of lymphoepithelioma-like carcinoma. Their true incidence of classic LCLC was 2.6%, although it was 5.7% with the 2004 WHO classification. With preliminary statistics, 32 patients were diagnosed as having LCLC at our institution between 1999 and 2016, accounting for 1.6% of the total lung cancer cases (1935 cases) during the corresponding time period. Though according to WHO 2015, the incidence of LCLC will decrease because tumors such as basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and rhabdoid phenotype carcinomas have been excluded from LCLC classification. Seven cases of lymphoepithelioma-like carcinoma cases, three clear cell variants cases, one rhabdoid variant case, two basaloid carcinoma cases, 27 cases of LCNEC, and 3 cases of combined LCNEC from our institution were excluded because of these new classifications.

Regarding tumor location, LCLCs mostly present as peripheral tumors, although they may be centrally located. In gross examination they frequently appear as large necrotic tumors [7,9,10,12]. In our study, tumors were centrally located in 6 (18.75%) patients, 26 (81.25%) patients had peripheral lesions.

The diagnosis of LCC can only be made on a sampled resected tumor and it is nearly impossible to diagnose LCLC from preoperative biopsies. In preoperative small biopsies, in the setting of a tumor with a negative adenocarcinoma marker (i.e., TTF-1) and only weak or focal staining for a squamous marker, it is best to classify the tumor as 'NSCLC, not otherwise specified (NOS). In our study, a malignant tumor was confirmed in 5 (15.6%) patients via bronchoscopic biopsy, and in 15 (46.87%) patients using CT-guided transthoracic needle biopsy, and diagnosis of a malignant tumor was achieved by FS examination in 12 (37.5%) patients during the operation.

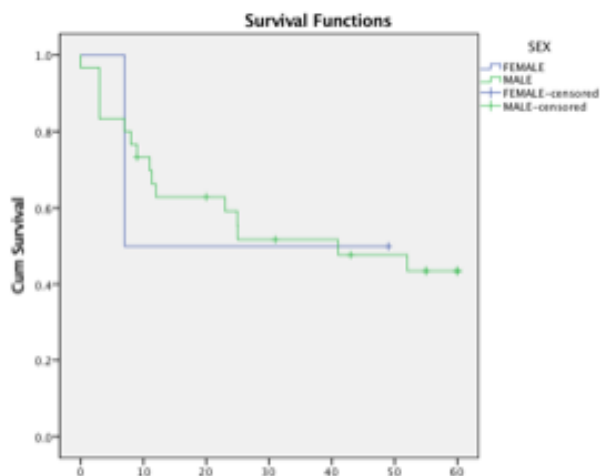
The treatment of LCLC is comprehensive, primarily with complete tumor resection with systematic nodal dissection [13]. In Liang et al.'s study, the radical resection rate of LCLC was 73.5%, of which the majority underwent a lobectomy and the patients with classic LCLC had a significantly higher one-year survival rate (74.4%). Whether adjuvant chemotherapy is required

following surgery remains controversial [7,13]. We performed complete tumor resection with systematic nodal dissection in our 29 patients because of LCLC over the 15 years. In the other 3 patients, one had N2 lymph node metastasis, which was confirmed with mediastinoscopy, and no further surgical resection was applied. The patient gave up curative chemoradiotherapy. One patient who had lobectomy with chest wall resection with positive surgical margins had adjuvant chemoradiotherapy, and the remaining patient had stage IV disease and underwent surgery for diagnostic reasons and prolonged air leakage after transthoracic needle biopsy. Pneumonectomy, bilobectomy inferior, lobectomy and lobectomy with resection of the chest wall was performed for patients with complete tumor resection. There was a recurrence in a patient with pleural invasion, 2 months after surgery on the diaphragm, anterior of the thoracotomy incision, in the posterolateral and retrosternal areas. In spite of chemoradiotherapy, the patient died in the postoperative 3rd month. In one patient who underwent lobectomy and chest wall resection after neoadjuvant chemotherapy, metastasis on the both two adrenal glands, pancreas, liver, anterior wall of the abdomen, abdominal lymph nodes, and intestinal segments was determined and the patient died four months later. However, the other patients had no distant organ metastasis or local recurrences.

The 1, 3, and 5-year survival rates of our study were 65.6%, 53.1%, and 46.9%, respectively. The 5-year survival rates were reported in the literature as between 46.7% and 61.5%, but these studies were based on the 2004 WHO classification. In our current study, we present our survival rates and survival curves for the 2015 WHO classification with a more homogeneous LCLC group (Table 3 and Graph 3). Furthermore, 23 of the 32 patients with advanced-stage LCLC underwent oncologic therapy, two received neoadjuvant chemotherapy, 17 received adjuvant chemotherapy, and 4 had chemoradiotherapy. A total of 3 patients had palliative radiotherapy.

Table 3 . Survival rates and survival curves for the 2015 WHO classification

	Total number of patients	Number of patients died	Number of patients alive	%
Female	2	1	1	50.0%
Male	30	16	14	46.7%
Overall	32	17	15	46.9%



Graph 3. Survival rates and survival curves for the 2015 WHO classification.

The role of adjuvant therapy for LCLC should be examined in large-center prospective, randomized trials. LCLCs were characterized by extensive local and distant tumor spread, particularly to extrathoracic organs such as the kidneys, adrenal glands, liver, gastrointestinal tract and mesentery, and extremely short survival. Despite surgery and adjuvant chemoradiotherapy, LCLCs are aggressive with a poorer prognosis compared with other pulmonary cancers. Our study showed that if the LCLC is treated with a multimodal approach and metastasis is not observed, survival is promising.

As a conclusion the diagnosis of LCLC is primarily based on the pathologic diagnosis. Several changes have occurred that increase the clinical significance of LCLC histopathologic classification. We compared our findings with the literature published before the 2015 WHO Classification of Tumors of the Lung. Thanks to the 2015 WHO classification, the definite diagnosis rate of LCLC has improved, and developments in epidemiologic, biologic, and therapeutic trials are promising.

Declaration of conflicting interests

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

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Original Article

The effect of polyglycolic acid mesh application in tracheal anastomoses on pressure and tensile strength: an ex vivo experimental study

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ABSTRACT

Background: This study aims to investigate the effect of polyglycolic acid (PGA) mesh application in tracheal anastomosis on the air-leakage and tension resistance.

Materials and Methods: Tracheae were collected from freshly slaughtered healthy sheep weighing 25-30 kg (2-3 years old) that were acquired from the local slaughterhouse. Twenty-eight tracheae were transported to the laboratory within an hour of slaughter and then dissected to remove the esophagus before obtaining 20-cm long tracheae. All tracheae were transected at the midpoint. In Groups 1 and 2, the transected tracheae were anastomosed by using interrupted 3-0 Vicryl sutures. In Groups 3 and 4, after anastomosing the transected tracheae with interrupted 3-0 Vicryl, the sites of anastomosis were reinforced by using Polyglycolic acid mesh. Groups 1 and 3 were tested for tensile strength, while Groups 2 and 4 were tested for pressure resistance.

Results: The median pressure was 49.00 ± 7.47 mmHg in the group anastomosed with only Vicryl, whereas it was measured as 70 ± 13.49 mmHg in the group on which the anastomoses were reinforced with PGA mesh. The median force needed to break anastomoses were 166.40 ± 24.28 Newton in the Vicryl-only group and 136.80 ± 34.93 newton in the PGA- reinforced group. The difference between the pressure resistance values of the Vicryl-only group and the PGA reinforced group was significant ($p = 0.006$). However, the difference with regard to the tensile strength was insignificant ($p = 0.201$).

Conclusion: We found that the reinforcement of the anastomosis site with polyglycolic acid mesh significantly increases the pressure resistance but does not significantly affect tensile strength.

Key Words: trachea, anastomoses, polyglycolic acid

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Introduction

Tracheal resection is performed most commonly for benign disorders. The primary indication is fibrotic stenosis, whether idiopathic, traumatic, or post intubation. Occasionally, tracheal resection is indicated for neoplastic diseases or short-segment malacia [1]. Tracheal resection and end-to-end anastomosis has proven to be a successful procedure in the management of post-traumatic stenosis and benign tracheal neoplasia [2].

The most common complications associated with tracheal resection include dehiscence of the anastomosis, granulation tissue formation, and subcutaneous emphysema [2]. Complications that arise from tracheal surgery may result in re-stenosis, and therefore, it is important to prevent these complications. Many clinical and experimental studies have been conducted on reinforcement of the anastomosis. Polyglycolic acid (PGA) mesh is a biodegradable material which consists of PGA layers and oxidized cellulose mesh. Its long-term effects are not clear yet. Although PGA mesh has been used in the lung parenchyma to prevent air leakage, its application in tracheal surgery is not common [3,4].

We aim to investigate the effect of PGA mesh application on air leakage and tensile durability in tracheal resection and end-to-end anastomosis.

Materials and Methods

Because this study was a laboratory-based study with no living subjects, institutional review board approval was not necessary. Tracheae were collected from freshly slaughtered healthy sheep weighing 25-30 kg (2-3 years old) that were acquired from the local slaughterhouse. Twenty-eight tracheae were transported to the laboratory within an hour of slaughter and then dissected to remove the esophagus before obtaining 20-cm long tracheae. Twenty-eight tracheae were divided into four groups each of which was comprised of seven tracheae. All tracheae were transected at the midpoint, through two tracheal rings. The internal and external diameters of the tracheae were measured at the site of transection transversely.

In Groups 1 and 2, the transected tracheae were re-anastomosed by using interrupted 3-0 Vicryl sutures (Medeks, Istanbul, Turkey), with a gap of 3-4 mm in between the sutures. In Groups 3 and 4, after re-anastomosing transected tracheae with interrupted 3-0 Vicryl, the sites of anastomosis were reinforced by using polyglycolic acid mesh (Neoveil, Gunze, Ayabe, Japan). The

polyglycolic acid mesh, 1 cm in width, was wrapped all around the anastomosis and sutured with 3-0 Vicryl at four points of the anastomosis (Figure 1).



Figure 1. The anastomosis was reinforced with PGA that was rolled 1 cm width at four points in groups 3 and 4.

Groups 1 and 3 were subjected to tensile strength experiments and Groups 2 and 4 were subjected to pressure experiments. The tensile strength experiment was performed by using an electronic spring scale, with the force needed to break anastomosis being recorded [5] (Figure 2). For the pressure experiment, a sphygmomanometer was attached to a cuffed 8.5 mm endotracheal tube, with the pressure at air leakage observed being recorded [5] (Figure 3). SPSS for Windows (version 17.0, IBM, Armonk, New York) was used for statistical analysis. All data are presented as the mean $\pm$ standard deviation. Comparison between group means was carried out using the Mann-Whitney U test at a significance level of $p < 0.05$.



Figure 2. Scaling the tensile strength by an electronic spring scale.

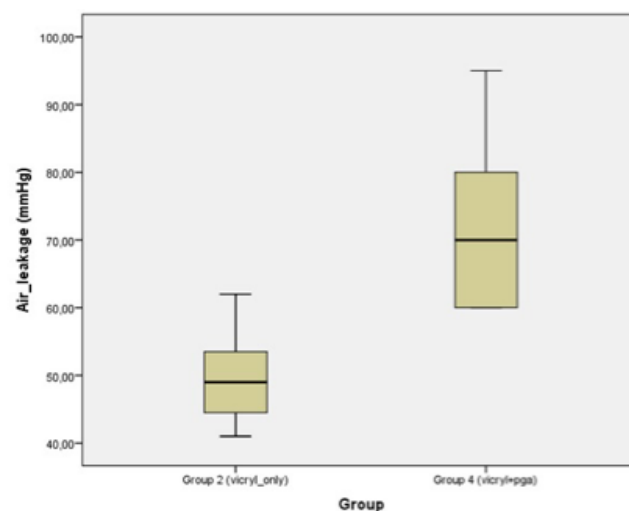


Figure 3. Comparison of groups in air leak pressure by sphygmomanometer.

Results

The median transverse and the anteroposterior diameter of the pressure group and the tension group were 18.00 ± 2.29 SD, min 16-max 23, and 18.00 ± 1.67 SD, min 16-max 20; 18.00 ± 1.41 SD, min 17-max 21, and 18.00 ± 2.69 SD, min 15-22, respectively. The amount of mean force required to break off the anastomoses was 166.40 ± 24.28 newton (min 132.70 newton-max 206.50 newton) in group 1 (Vicryl only), and 136.80 ± 34.93 newton (min 113.90 newton-max 201.40 newton) in group 3 (Vicryl + PGA) (Figure 4).

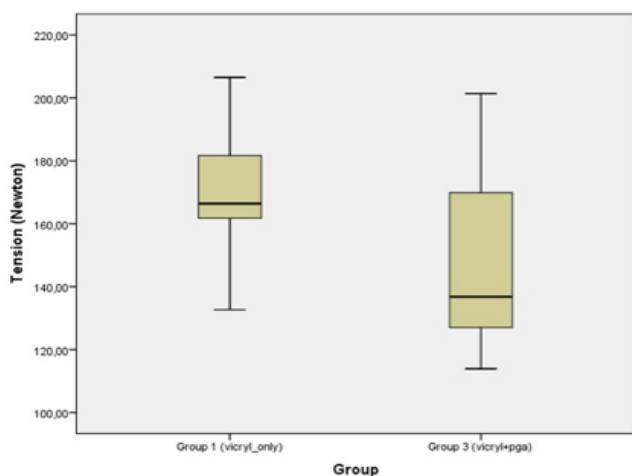


Figure 4. Results of tensile strength experiment.

There was no significant difference between group 1 and group 3 with respect to the mean force required to break off the anastomoses ($p = 0.201$). In the pressure experiment, the mean pressure resulting in air leakage was 49.00 ± 7.47 mmHg (min 41mmHg-max 62 mmHg) in group 2 (Vicryl only) and 70.00 ± 13.49 mmHg (min 60 mmHg-max 95 mmHg) in group 4 (Vicryl + PGA) (Figure 5). The mean pressure required to cause air leakage was significantly higher in group 4 compared to group 2 ($p = 0.006$).



Figure 5. Scaling the air leakage by a specific manometer.

Discussion

Our results demonstrated that air leakages in the anastomotic region which is one of the most serious complications of tracheal anastomoses sutured with Vicryl and supported with a PGA sheet can be overcome. Nonetheless, this was not the case as far as the breaking force was concerned. PGA support failed to increase the breaking force in our experiment. The length of adult trachea depends on the age, gender, and genetic characteristics of the individual. Its average length is 11 cm in adult males and 10 cm in adult females. In adults the mean value of the internal transverse diameter has been reported as 2.3 cm and the internal antero-posterior diameter as 1.8 cm [6,7]. The measured length of the sheep trachea used in our study was between 15 cm and 20 cm.

In tracheal anastomoses procedure, the surgical field is filled with saline to control air leakage after completion of the anastomosis. This control measure is done under 30-40 mmHg ventilation pressure when the cuff of the intubation tube is deflated and the patients mouth and nose are obstructed. Any air leakage detected must be repaired. The pediculated strap muscle flap can be used to reinforce the anastomosis line. Placement of a chin-to-chest suture for seven days postoperatively is also recommended to prevent extension of the neck. The site of anastomosis must be re-evaluated in cases of subcutaneous emphysema or air leakage through drainage catheter, which would either be a minimal dehiscence or a life-threatening separation of the anastomosis. Both must be repaired and a muscle flap must be used. [9]. The median pressure required to cause air leakage was 49.00 ± 7.47 mm Hg in the group in which the anastomosis was performed only with sutures, whereas it was 70 ± 13.49 mmHg in the group in which the anastomosis was performed with sutures and PGA mesh.

Polyglactin (Vicryl) and polydioxanone are commonly used suture materials for the different techniques of tracheal anastomosis. Primary anastomosis with interrupted 3/0 or 4/0 Vicryl sutures is the most preferred approach in tracheal stenosis [2,8,10]. After the resection, two traction sutures are usually placed on both sides of the proximal and distal trachea. Vicryl sutures are then placed one by one, leaving the knots outside the tracheal lumen. Proximal and distal traction sutures are used to feel the tension. There is no way to determine the acceptable tension other than the experience

of the surgeon [1]. In our study, in order to preserve the cartilages, the tracheae were transected at the midpoint, through two tracheal rings. End-to-end anastomosis was performed by using interrupted 3/0 Vicryl sutures. PGA mesh is a bio-degradable material composed of polyglactic acid sheets and oxidized cellulose mesh. It is a synthetic, absorbable material which is used for tissue reinforcement.

Although its long-term effects are not clear, it is used in lung surgery to prevent parenchymal air leakage. However, until now, its effects on tracheal surgery have not been reported. PGA mesh is not only used in lung surgery but also in pancreas and spinal surgery as well to prevent leakage [3,4,11,12]. It is also used in liver surgery to prevent bile leakage [13]. To the best of our knowledge, there are no reports in the literature on the use of PGA mesh in tracheal surgery. Nevertheless, it has been reported that the use of PGA mesh in iatrogenic injuries of the distal trachea and main bronchus shows promising results [14]. PGA mesh is most commonly used in the lung parenchyma to prevent air leakage with or without fibrin glue. Its application in pneumothorax with Video Assisted Thoracic Surgery (VATS) has been reported to decrease complications like air-leakage and recurrence of pneumothorax. Its use on the site of the staple may prevent air-leakage, new bulla formation and recurrences [3]. As cautioned against in the study just cited, chemical pleurodesis and fibrin glue are not used in young patients with pneumothorax. Additional studies may help to better understand the effects of PGA mesh.

Air leakage is common complication of lung parenchymal surgery, and it is one of the most common causes of morbidity after lung resection [15,16]. Persistent air leakage for more than five days may result in atelectasis, pneumonia, and empyema [17]. Despite the use of different surgical techniques and materials to decrease air leakage, it still has a high incidence. It is observed in 48-70 % of the cases intraoperatively and may persist for more than seven days in 15-18% of the cases. There is still no ideal method for prevention [18]. The literature shows that PGA has been used with fibrin glue for pulmonary air leakage. Fibrin glue has been shown to be effective in the prevention of air leakage [19,20].

The reconstruction techniques applied for tracheal anastomoses after tracheal resection are similar to each other, but different tissues and materials are used to re-

inforce the anastomoses. For example, strep muscles, fibrin glue, bovine pericardium, Polytetrafluoroethylene (PTFE), and PGA+fibrin glue are some of the materials and tissues used [9,21].

In a previous ex-vivo study, it was reported that the application of n-butyl-2-cyanoacrylate to the site of the anastomosis in the trachea had beneficial effects in terms of intraluminal pressure. However, another study on rats revealed this application's inflammatory effects, which may undermine its usage in vivo [5,22].

In conclusion, while different techniques to reinforce tracheal anastomoses are still under investigation, our study was nonetheless able to show that PGA mesh may be an effective method to reinforce tracheal anastomoses for the prevention of air-leakage. However, further clinical and experimental investigations are still needed for confirmation of these effects.

Declaration of conflicting interests

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

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Original Article

The role of fluids in postpneumonectomy pulmonary edema: an experimental study

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ABSTRACT

Background: The role of fluids in the etiology of postpneumonectomy pulmonary edema (PPE) is controversial. The aim of this experimental study was to assess the effect of crystalloid or colloid fluids and normal or high volume on the etiology of PPE.

Materials and Methods: 20 New Zealand rabbits were used and divided into 4 groups. Pneumonectomy had performed firstly in each subject, then for 3 hours, normal and high volume of crystalloid and colloid fluids were administered. The first group were administered 3 ml/kg/h crystalloid (0.9% NaCl), the second group received 10 ml/kg/h of the same crystalloid, the third group were administered 3 ml/kg/h colloid (6% HES/0.7) and the fourth group received 10 ml/kg/h of the same colloid infusion. Pneumonectomy and remaining lung materials were weighed when wet and dry and pathologic investigation was performed with a light microscopy.

Results: There was no significant difference between the preoperative and postoperative wet/dry ratio (W/DR) of pneumonectomy and remaining lung material in all groups administered crystalloid and colloid (1st Group $Z = 0.707$; $p = 0.480$, 2nd Group $Z = 0.577$; $p = 0.564$, 3rd Group $Z = 0.577$; $p = 0.564$, 4th Group $Z = 0.677$; $p = 0.498$). There was no significant difference identified between pneumonectomy material W/DR for all crystalloid and colloid groups ($x^2 = 2.787$; $p = 0.426$) and again between the remaining lung material W/DR ($x^2 = 2.858$; $p = 0.414$). The histopathologic assessments of all groups were similar.

Conclusion: Administration of crystalloid or colloid fluids at normal or high volume was assessed not be responsible alone for the PPE etiology in subjects with normal cardiac function. Histopathologic findings were similar in all groups.

Key Words: pulmonary edema, pneumonectomy complications, pulmonary resection

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Introduction

Pulmonary edema (PE) was first described by Gibbon and Gibbon in 1942 in their study of cats [1]. PE may form due to any factor causing pulmonary interstitial fluid pressure to increase from negative values to positive values. The most common cause of PE not due to cardiac sources is disruption or destruction of pulmonary capillary membrane [2]. Factors causing increases in pulmonary capillary hydrostatic pressure or damaging alveolocapillary membrane may cause PE. With pneumonectomy, vital capacities fall by 35-40%. Fluid accumulation in the remaining lung fills the interstitial field and alveoli with fluid causing surfactant inhibition. Thus, the ventilated pulmonary field reduces inducing serious hypoxia [3]. Fluid accumulation in the remaining lung leads to high rates of 4-5% postoperative mortality [4].

Non-cardiac sourced PE following pneumonectomy was first described by Zeldin et al. When first described the most important cause was excessive fluid loading [5]. Many experimental studies have been performed about the etiology of postpneumonectomy pulmonary edema (PPE) and other factors have been identified. Causes such as increased pulmonary capillary hydrostatic pressure, increased permeability, hormonal factors, mediastinal lymph node dissection and hyperinflation with ventilator treatment are reported [6]. Additionally, there are publications showing fluids do not play a role [7,8]. Thus, other mechanisms have been revealed while the role of fluids in PPE is still controversial.

In this study, our aim was to investigate whether non-cardiogenic PE is induced in the remaining lung in a rabbit model administered crystalloid and colloid fluids and different amounts of fluid after pneumonectomy.

Materials and Methods

A total of 20 New Zealand rabbits with a mean weight of 1.831 g (range, 1.400 to 2.900 g) were used in this study. All animals treated and cared for in accordance with the TU, Institutes of Health Guide for the care and Use of Laboratory Animals and the research was conducted in accordance with the 1964 Helsinki Declaration. The subjects were divided into four groups including five in each group. The first group was given 3 mL/kg/h of crystalloid (isotonic 0.9% NaClR, Fresenius Kabi AG, Bad Homburg, Germany) the second group was given 10 mL/kg/h of crystalloid (isotonic 0.9% Na-

ClR, Fresenius Kabi AG, Bad Homburg, Germany); the third group was given 3 mL/kg/h of colloid (6% HESR 450/0.7, Fresenius Kabi AG, Bad Homburg, Germany), and the fourth group was given 10 mL/kg/h of colloid (6% HESR 450/0.7, Fresenius Kabi AG, Bad Homburg, Germany). All groups received infusion for three h. The subjects were anesthetized with 10 mL/kg of ketamine (Ketalar 50 mg/mL, 10 mL flask, Phizer, Kent, UK) and 0.3 mL/kg xylazine hydrochloride (Rompun 50 mL flask, Bayer, Leverkusen, Germany) and placed in a supine position. The jugular veins of the subjects were dissected using a vertical incision on the neck. They were catheterized using 24F branule. 1 mg of ethylenediaminetetraacetic acid (EDTA) in 0.9 mL and 0.1 mL (TrasyloIR 10,000 U/mL, 50 mL flask, Bayer, Leverkusen, Germany) aprotinin-containing plastic tubes were prepared. 1 mL of blood was drained into these previously prepared and cooled. These blood samples were centrifuged at 2,000 g, -4°C for 30 min. Blood plasma was separated and kept at -30°C. After the blood was drawn, 3 mL/kg/h or 10 mL/kg/h crystalloid or colloid fluid were administered via a perfusion pump (Braun Perfusor, Melsungen, Germany).

Meanwhile, the trachea was reached and incised by expanding the incision to the neck. The subjects were intubated with a 3.0 intubation tube and were ventilated with continuous positive airway pressure with O₂ (tidal volume: 4 mL/kg; respiratory rate 45-60/min; positive airway pressure: 1-2, 30% O₂, Vokar- Sav: 0301). The rabbits were placed in lateral decubitus according to the side to which the pneumonectomy was to be applied. Posterolateral thoracotomy was applied to all subjects. The pulmonary inferior ligament was divided, then, isolated and the hilus was tied and cut en bloc with 2/0 silk, and pneumonectomy was performed.

In the first group, left pneumonectomy and right pneumonectomy were performed in three and two subjects, respectively. In the second group, left pneumonectomy and right pneumonectomy were performed in two and three subjects, respectively. In the third group, left pneumonectomy and right pneumonectomy were performed in three and two subjects, respectively. In the fourth group, left pneumonectomy and right pneumonectomy were performed in three and two subjects, respectively. The blood samples from the contralateral jugular vein were collected into plastic tubes, as described. The pneu-

monectomy procedure was repeated for the contralateral lung and all subjects were sacrificed.

For pathology of pneumonectomy and remaining lung material, a 2x2 mm biopsy was taken from the lower lobe posterobasal segment and immediately weighed with a sensitive scale when wet to prevent losses due to evaporation. Later pneumonectomy and remaining lung material were dried for 24 hours in an 80 °C oven and weighed again with the same scale, similar to the literature [8,9]. Both materials had W/DR and percentages identified. Material taken for pathology was left in formaldehyde and then assessed under a light microscope.

Statistical Analysis

The data were collected and analyzed using Excel software (Microsoft Corp, Seattle, WA). Descriptive statistics were used to report the means and standard deviations of the continuous variables and number and percent of categoric variables. The Kruskal-Wallis test was used to compare mean weight of the subjects. The Wilcoxon test was used to analyze significant differences in the pneumonectomy and remain lung W/DR levels. A p value of <0.05 was considered statistically significant.

Results

There was no significant difference in preoperative and postoperative hemogram values for subjects in all groups. With the aim of determining whether pulmonary edema developed after pneumonectomy and fluid replacement in subjects in the first group, the weighed lung W/DR results are given in table 1.

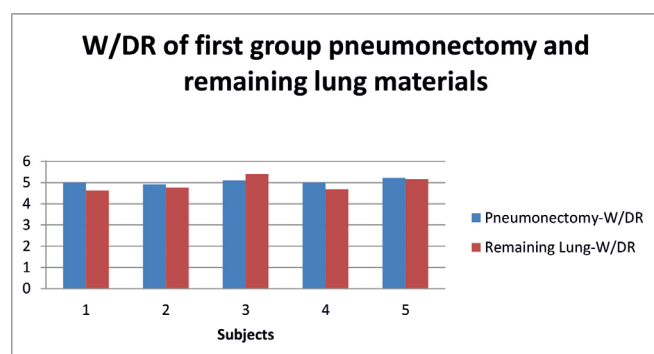
The initial lung specimen removed with pneumonectomy in the first group had mean wet weight of 3.1366 g (SD $\pm$ 1.57). The mean dry weight of pneumonectomy lungs was 0.6175 g (SD $\pm$ 0.30). The mean wet weight of the remaining lung was found to be 4.8305 g (SD $\pm$ 1.68). The mean dry weight of the remaining lung was identified as 0.9933 g (SD $\pm$ 0.38) (Table 1).

The pneumonectomy and remaining lung W/DR were 5.04 ± 0.11 (19.82%, SD $\pm$ 0.41) for pneumonectomy specimens and 4.93 ± 0.34 (20.36% $\pm$ 1.35) for remaining specimens (Table 1). The W/DR graph for the first group is shown in graph 1. There was no statistically significant difference between the W/DR in this group (Z = 0.707; p = 0.480).

Table 1. W/DR results for pneumonectomy and remaining lung material from the first (Cyrstalloid 3 ml/kg/h) group.

No	R/L	PNE/ WET	PNE/ DRY	PNE W/DR	%	R/L	REM/ WET	REM/ DRY	REM W/DR	%
1	L	1.83	0.36	5.00	20.00	R	6.74	1.45	4.63	21.58
2	L	1.12	0.22	4.91	20.35	R	6.56	1.37	4.76	21.00
3	L	3.66	0.71	5.10	19.61	R	3.95	0.73	5.40	18.50
4	R	4.52	0.90	5.00	20.00	L	3.32	0.70	4.68	21.36
5	R	4.54	0.86	5.22	19.15	L	3.56	0.69	5.16	19.37

R: Right, L: Left, Pne: Pneumonectomy, Rem: Remaining lung, W/DR: Wet/Dry Ratio



Graph 1. W/D R of first group pneumonectomy and remaining lung materials.

In the second group pneumonectomy and remaining lung material was weighed when wet and dry. The mean

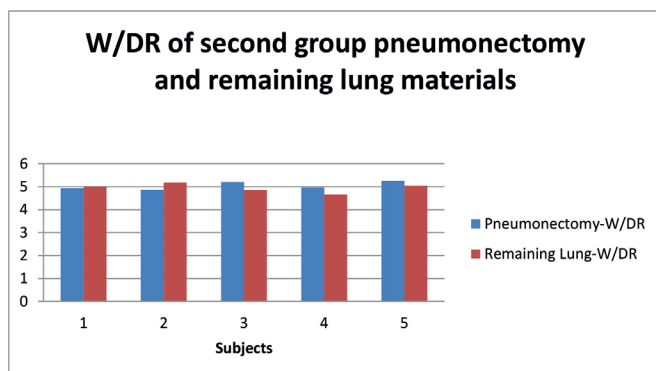
wet weight of pneumonectomy material was 4.1333 g (SD $\pm$ 1.35). The mean dry weight of pneumonectomy material was 0.8147 g (SD $\pm$ 0.24). The mean wet weight of remaining lung material was 3.8642 g (SD $\pm$ 1.3032) with mean dry weight of 0.7780 g (SD $\pm$ 0.24) (Table 2).

In the second group, pneumonectomy material W/DR was found to be 5.04 ± 0.18 (19.84%, SD $\pm$ 0.69) with remaining lung material W/DR of 4.95 ± 0.20 (20.24% SD $\pm$ 0.82) (Table 2). The W/DR graph for the second group is observed in graph 2. There was no statistically significant difference found between the materials for W/DR (Z = 0.577; p = 0.564).

Table 2. W/DR results for pneumonectomy and remaining lung material from the second (Cyrstalloid 10 ml/kg/h) group.

No	R/L	PNE/ WET	PNE/ DRY	PNE W/DR	%	R/L	REM/ WET	REM/ DRY	REM W/DR	%
1	L	2.09	0.42	4.93	20.27	R	5.06	1.01	5.00	20.00
2	L	3.42	0.70	4.86	20.59	R	4.88	0.94	5.18	19.30
3	R	5.27	1.01	5.20	19.23	L	4.45	0.91	4.85	20.63
4	R	4.70	0.94	4.96	20.14	L	2.47	0.53	4.66	21.46
5	R	5.15	0.97	5.26	19.00	L	2.44	0.48	5.04	19.84

R: Right, L: Left, Pne: Pneumonectomy, Rem: Remaining lung, W/DR: Wet/Dry Ratio

**Graph 2.** W/DR of second group pneumonectomy and remaining lung materials.

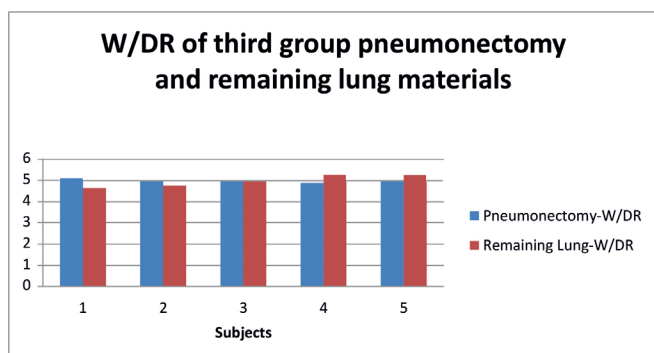
In the third group, the mean wet weight of pneumonectomy material was 4.0437 g (SD $\pm$ 1.13), with mean dry weight identified as 0.8071 g (SD $\pm$ 0.21). The mean wet weight of the remaining lung was 4.4818 g (SD $\pm$ 1.19) with mean dry weight found to be 0.890 g (SD $\pm$ 0.19) (Table 3).

The W/DR of pneumonectomy material in the third group was 5.00 ± 0.08 (19.99%, SD $\pm$ 0.31), while it was 4.99 ± 0.28 (19.99%, SD $\pm$ 1.13) for remaining lung material (Tables 3). The W/DR variation in the third group is shown in Graph 3. There was no statistically significant difference in the W/DR of the two materials ($Z = 0.577$; $p = 0.564$).

Table 3. W/DR results for pneumonectomy and remaining lung material from the third (Colloid 3 ml/kg/h) group.

No	R/L	PNE/ WET	PNE/ DRY	PNE W/DR	%	R/L	REM/ WET	REM/ DRY	REM W/DR	%
1	R	4.84	0.94	5.11	19.57	L	3.25	0.69	4.65	21.48
2	R	4.63	0.92	5.00	20.00	L	3.12	0.65	4.76	21.00
3	R	5.10	1.02	5.00	20.00	L	5.06	1.01	5.00	20.00
4	L	2.79	0.57	4.89	20.46	R	5.51	1.04	5.27	18.99
5	L	2.83	0.56	5.00	20.00	R	5.45	1.03	5.26	19.00

R: Right, L: Left, Pne: Pneumonectomy, Rem: Remaining lung, W/DR: Wet/Dry Ratio

**Graph 3.** W/DR of third group pneumonectomy and remaining lung materials.

pneumonectomy material was 3.127 g (SD $\pm$ 0.47) with mean dry weight of 0.630 g (SD $\pm$ 0.09). The mean wet weight of the remaining lung material was 3.1038 g (SD $\pm$ 1.09) with mean dry weight identified as 0.597 g (SD $\pm$ 0.19) (Table 4).

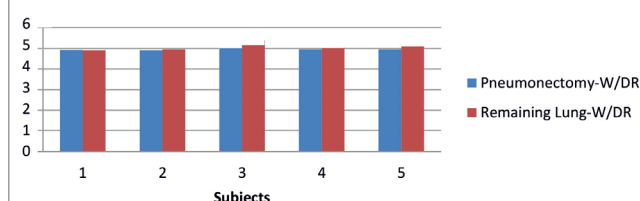
In the fourth group, pneumonectomy material W/DR was 4.95 ± 0.05 (20.17%, SD $\pm$ 0.20), with remaining lung material W/DR of 5.02 ± 0.09 (19.90%, SD $\pm$ 0.38) (Table 4). The variations in W/DR in the fourth group can be seen in graph 4. There was no statistically significant difference in W/DR in both materials ($Z = 0.677$; $p = 0.498$).

In the fourth group, mean wet weight of

Table 4. W/DR results for pneumonectomy and remaining lung material from the fourth third (Colloid 10 ml/kg/h) group.

No	R/L	PNE/ WET	PNE/ DRY	PNE W/DR	%	R/L	REM/ WET	REM/ DRY	REM W/DR	%
1	L	2.76	0.56	4.91	20.37	R	4.15	0.84	4.90	20.40
2	L	3.14	0.64	4.90	21.41	R	4.23	0.85	4.97	20.09
3	L	2.55	0.51	5.00	20.00	R	3.52	0.68	5.14	19.43
4	R	3.61	0.72	4.98	20.08	L	2.68	0.53	5.01	19.96
5	R	3.56	0.71	5.00	20.00	L	2.69	0.53	5.09	19.63

R: Right, L: Left, Pne: Pneumonectomy, Rem: Remaining lung, W/DR: Wet/Dry Ratio

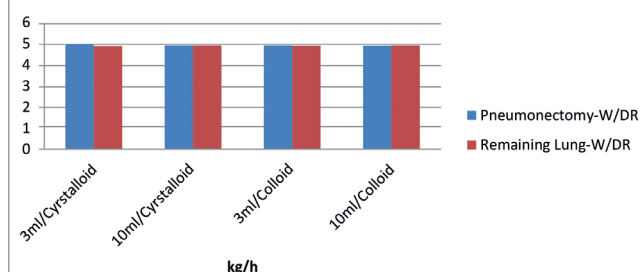
W/DR of fourth group pneumonectomy and remaining lung materials**Graph 4.** W/D R of fourth group pneumonectomy and remaining lung materials.

The mean W/DR for pneumonectomy material in all isotonic and colloid groups were 5.04 (19.82%, SD $\pm$ 0.45), 5.04 (19.84%, SD $\pm$ 0.69), 5.00 (20.00%, SD $\pm$ 0.31), and 4.95 (20.17%, SD $\pm$ 0.20), respectively. There was no statistically significant difference between these ratios ($\chi^2 = 2.787$; $p = 0.426$). Again, in the isotonic and colloid groups, the mean W/DR for remaining lung material after pneumonectomy were 4.93 (20.36%, SD $\pm$ 1.35), 4.95 (20.24%, SD $\pm$ 0.82), 4.99 (20.09%, SD $\pm$ 1.13), and 5.02 (19.90%, SD $\pm$ 0.38), respectively. There was no statistically significant difference found between these rates ($\chi^2 = 2.858$; $p = 0.414$). All results can be seen in table 5. The relationship between the groups can be seen in graph 5.

Table 5. Comparison of W/DR for pneumonectomy and remaining lung material in all groups.

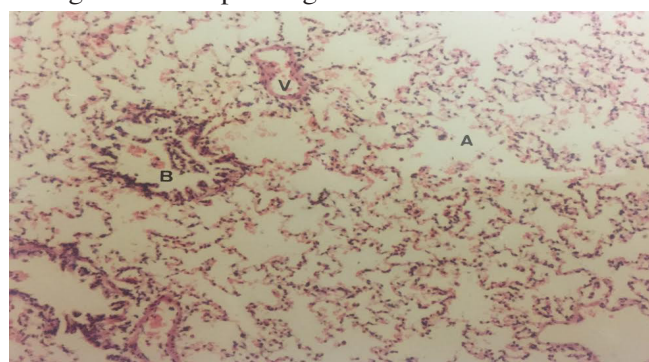
Groups	Fluid Dose	Pne W/DR	%	SD	Rem W/DR	%	SD
1	Crystalloid 3ml/kg/h	5.04	19.82	0.45	4.93	20.36	1.35
2	Crystalloid 10ml/kg/h	5.04	19.84	0.69	4.95	20.24	0.82
3	Colloid 3 ml/kg/h	5.00	20.00	0.31	4.99	20.09	1.13
4	Colloid 10 ml/kg/h	4.95	20.17	0.20	5.02	19.90	0.38

Pne: Pneumonectomy, Rem: Remaining lung, W/DR: Wet/Dry Ratio, SD: Standard Deviation

W/DR in all groups**Graph 5.** W/DR in all groups.

Histopathologic assessment with a light microscope observed common widening of alveoli in all groups. Slight fragmentation of alveoli septa, widening of capillary walls and occasional fragmentation along with minimal hemorrhage within alveoli were observed. As a result, intraalveolar erythrocyte and focal congestion

were identified. Additionally, in the interstitial field and normal alveoli, congestion and edema with fluid findings were not encountered. Fragmented alveoli structure due to positive ventilation can be seen under the light microscope in figure 1.

**Figure 1.** The overview of fragmented alveoli structure under the light microscope.

Discussion

General anesthetic agents have hypotensive effects. Since Ringer solution (100 L ringer at equal levels to 1 L blood) was identified to be able to carry O₂, clear fluid loading was begun in operations [6]. However, later studies have revealed that fluid loading may cause some complications. As a result, investigating the contribution to the development of PE of administration of crystalloid and colloid fluids at normal or high volumes in pneumonectomy carries great importance.

For development of PE, meaning filling of alveoli with fluid in experimental and clinical studies, the lung needs to contain 50-100% more fluid than normal (10). For PE formation, the wet lung/body weight ratio must exceed 0.01 or the upper limit of 0.012 [11]. Additionally, a more certain parameter is the wet/dry ratio (W/DR) of the lung which is normally 5.13 in experimental animals but is accepted as above 5.2 in humans [12]. In this study, the pneumonectomy and remaining lung materials were assessed with W/DR based on values in the literature.

Pneumonectomy and remaining lungs of subjects from the first group had fluid loading at normal volumes and there was no statistically clear increase in W/DR leading to consideration of pulmonary edema. In the second group, in spite of high-volume crystalloid leading after pneumonectomy, there was no statistical difference W/DR in the remaining lung and fluid did not accumulate. In the third group, normal volume of colloids were administered after pneumonectomy, the W/DR in the remaining lung did not increase significantly and congestion was not observed. In the fourth group, high volume of colloid replacement after pneumonectomy did not cause edema in the lung. These results for all groups comply with the literature [9,13].

Zeldin et al. in studies describing non-cardiogenic postpneumonectomy edema administered high volumes of fluids to dogs after pneumonectomy. After this, they identified increased cardiac output and pulmonary artery pressure. As a result, dogs administered excessive fluids developed PE [5]. Especially after right pneumonectomy, the remaining left lung has only 45% of total pulmonary flow and less lymphatic capacity. As a result of high fluid volume loading, there are publications stating edema is caused by increased cardiac output and increased net fluid filtration in pulmonary capillaries [14-16]. Shapira

et al. in a publication presenting two cases with PPE identified excessive fluid loading in both cases. They proposed excessive fluid loading was a risk factor [17].

Waller et al. retrospectively screened 402 cases and identified PE in 11 cases. It developed in 5.1% of right pneumonectomies, 4.0% of left pneumonectomies and 1% of lobectomies. Fluids received by patients developing PE were not identified to be excessive when compared to those not developing PE [18]. Again, a study by Turnage and Lunn retrospectively screened 806 pneumonectomy cases and identified PPE in 21. These cases were identified not to have received more fluid than the other pneumonectomy cases [19]. These results comply with our study results.

Lewis et al. identified no associations of right ventricle ejection fraction with pulmonary artery pressure or pulmonary vascular resistance when linked to the pulmonary artery. The volume of pulmonary vascular capacity was revealed to be sufficient to prevent increased pulmonary artery pressure due to increasing volume [20]. Thus, as increasing pulmonary vascular capacity due to excessive fluids can be tolerated, it does not contribute to edema formation.

Lee et al. increased the left atrial pressure in dogs with a balloon catheter. Later they performed pneumonectomy and measured extravasated fluid amounts in the lung. When left atrial pressure was increased by 5 mmHg before and after pneumonectomy, they observed fluid accumulated in the lungs. However, pneumonectomy did not affect fluid accumulation. As a result, they stated that hemodynamic changes did not cause fluid accumulation in the remaining lung after pneumonectomy [21].

Little et al. compared mediastinal lymph node dissection in dogs with pneumonectomy performed to dogs with normal lymph flow. As a result, lymph flow increased up to 10 times; however, this was the limit. If this limit was exceeded, they identified fluid accumulation began in the interstitium of the remaining lung [9]. Additionally, there are studies stating lymph flow is not affected by varying mediastinal lymph node dissection [22]. In our study, the most important reason for edema not forming in the remaining lungs of groups administered high-volume fluids may be adaptation of the lymphatic system.

Assaad et al. stated that though there are publications showing acute lung injury reduced with colloid fluids after lung resection, increasing oncotic pressure may cause renal failure due to kidney hypoperfusion and increase morbidity. They decided the most appropriate regime was colloids along with crystalloids [23].

The lungs are a metabolically active organ. Synthesis of vasoactive agents such as vasoconstrictor agents like angiotensin II or vasodilator agents like bradykinin, kallikrein and prostaglandin occur in the lungs. Van et al. proposed that release of these agents at high volume in the remaining lung after pneumonectomy causes metabolic balance changes [24]. Mathru et al. reported that if edema fluid and serum protein rates >0.6 in patients developing PE after pneumonectomy, it was linked to permeability increase [25]. Leukotrienes, platelet activating factor and some cytokines increase pulmonary capillary pressure without increasing capillary permeability and are proposed to be a major cause of PPE formation [2,7,26]. These results bring to mind the idea that the role of fluids in PPE may be found in metabolic events.

Pang et al. in an experimental study proposed hyperinflation increased fluid flow to the lung [27]. They identified that excessive alveolar distension causes widening of the intercellular interval in capillary endothelium easing fluid and protein leak. Administration of excessive fluids is controversial in PPE; however, they proposed that as there is no third cavity in the chest, fluid limitation is appropriate at present and hyperinflation should be avoided especially in right pneumonectomy to prevent mediastinal shifting [28]. Farkas et al. identified that lying position after pneumonectomy was associated with PPE [29].

In our study, no PE findings were encountered in wet and dry lungs during histopathologic investigation. Sometimes after pneumonectomy, tidal volume apply to both lungs may be applied to a single lung. This may cause barotrauma to the remaining lung. Again, hyperinflation of the remaining lung was identified to cause increased blood flow and pulmonary vascular resistance [26]. Our study assessed this aspect and continuous positive pressure administered to both lungs was administered in the same amount to the single lung after pneumonectomy. The result of this was that though mild levels of alveolar fragmentation, accompanied by

minimal hemorrhage in the interstitial area and alveoli was observed histopathologically, as the interstitial field was empty, alveoli did not fill with fluid and edema formation was not observed due to widening. It is considered the pathologies present were linked to hyperinflation. Hyperinflation may cause barotrauma; however, it was revealed not to be sufficient alone to cause PPE formation.

As pulmonary artery pressure, pulmonary vascular capacity, pulmonary capillary wedge pressure and left atrium pressure measurements were not performed, this limits the study of the role of different fluids and doses in PPE formation.

As a conclusion, in all groups administered crystalloid and colloid fluids, at normal and high volume, no significant difference was identified in W/DR of pneumonectomy and remaining lung materials. Histopathologically, all groups had equal amounts of alveolar widening and occasional fragmentation with minimal interstitial and alveolar hemorrhage observed. These histopathological results are caused by hyperinflation. Administration of crystalloid or colloid fluids at normal or high volume is considered insufficient alone to cause PPE etiology in subjects with normal cardiac functions.

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Declaration of conflicting interests

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Original Article

Is delayed puberty a new etiological factor for primary spontaneous pneumothorax?

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ABSTRACT

Background: Although the etiology of primer spontaneous pneumothorax (PSP) is not exactly understood, it has been suggested to be associated with rupture of bulla/bleb formations at the lung apices in thin, tall, young adults. In this study, we aim to evaluate whether delayed puberty is a new etiological factor for PSP.

Materials and Methods: A total of 91 patients who were treated for PSP in our clinic between January 2013 and September 2016 and who were scheduled for a follow-up visit by phone call and underwent pubertal-stage assessment were retrospectively analyzed.

Results: Of all patients, 10 (12.1%) were females and 81 (87.9%) were males. The mean age was 25.90 ± 6.83 (range, 17 to 38) years and the mean height was 178.90 ± 7.6 (range, 161 to 197) cm. The mean age at menarche of female patients was 14.20 ± 1.31 (range, 12 to 17) years. The women had a late age at menarche compared to the overall Turkish female population ($p < 0.0001$). The mean age for the development of facial hairs in the men was 16.63 ± 1.69 (range, 13 to 22) years, showing a later age, compared to the overall Turkish male population ($p < 0.0001$).

Conclusion: Our study results showed that the patients with pneumothorax had an advanced age at puberty, compared to the normal overall population, and that the pubertal growth spurt occurred within a short period of time. This condition is also suggested to have an effect on the lung maturity and the development of pneumothorax.

Keywords: primer spontaneous pneumothorax, pubertal growth, lung maturity

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Introduction

Spontaneous pneumothorax refers to a condition where there is accumulation of air in the pleural space in the absence of trauma. The condition is termed primary spontaneous pneumothorax (PSP) when there is no underlying pulmonary disease, which is observed in one per 5.8 to 16.7/100000 individuals of the overall population [1]. Although the etiology is not well-understood, it has been suggested to be associated with rupture of bulla/bleb formations at the lung apices in young, tall, and mostly thin adults [2]. Cigarette smoking is thought to play a role in its etiology; however, there is no definite opinion as to the mechanism of action [3]. Mortality is reported to be low; however, it is considered as a disease with a high mortality rate, taking into consideration that it has a recurrence rate of 16 to 52% [1,4].

Retrospective evaluation of the structural development and delayed puberty is a condition performed by observing the age at menarche in girls, and growth spurt, and age for facial hair development in boys. The growth rate is known to be small and pubertal spurt is delayed for about 2 to 4 years in cases with delayed puberty, compared to normal pubertal years. During pubertal spurts, the annual growth rate is observed to be lower than that of the normal population; however, the duration of pubertal spurt is prolonged. Growth recorded during pubertal spurts is known to be about 2.9 cm smaller than normal children. Sudden increase in height is expected, since there is a shorter duration of pubertal spurt, and is observed six-fold more in boys than girls [5-7].

Pneumothorax is observed six times more in males with delayed structural development. Besides, it is reported to be shown by conditions closely associated with growth and development such as tall height. Based on this relationship, a history of delayed puberty and late growth should be obtained in the life young adults who present with a diagnosis of pneumothorax. The aim of this study is to bring a new perspective to the etiology of PSP, and to review conditions of growth and development of the cases involved.

Materials and Methods

A total of 266 patients who were treated for PSP in our clinic January 2013 and September 2016 were retrospectively evaluated. Patients with syndromic

features and those with a history of familial pneumothorax were excluded from the study. The remaining patients were requested by phone to come for follow-up visits. A total of 91 patients who accepted to re-visit for follow-up were retrospectively subjected to the pubertal-stage assessment, developed by J Kaiser et al. [8]. In addition to demographic characteristic of participants, development of facial hairs in boys and the age at menarche in girls was evaluated. Due to the absence of the growth chart of the participants, they were questioned about height conditions during the age range of 12 to 15 years and 15 to 18 years, and also if they experienced conditions of delayed puberty and growth. Data on pubertal development and rate of puberty were obtained. The height (Ht) was measured in a standing position with bare feet using a portable measuring device (SECA 284), and was compared with puberty and pubertal growth of healthy Turkish children.

Statistical Analysis

Data analysis was performed using SPSS version 18.0 for Windows. Descriptive statistical variables were expressed in mean $\pm$ standard deviation (mean $\pm$ SD) and median range (minimum-maximum). Categorical data were presented as number (n) and percentages (%). The normality of distribution of data was evaluated with the Shapiro-Wilk test and parametric methods were performed to analyze variables which were in normal distribution and equal variance, whereas nonparametric methods were performed to analyze variables which were in normal distribution and unequal variance. The Mann-Whitney U-test and chi-square tests were performed for variables that were not normally distributed while One-way ANOVA was performed for associated samples. "p" values <0.05 were considered statistically significant with a confidence level of 95%.

Results

Of all participants, 10 (12.1%) were females and 81 (87.9%) were males. The mean age was 25.90 ± 6.83 (range, 17 to 38) years and the mean height was 178.90 ± 7.6 (range, 161 to 197) cm. The mean height of the men was 179.8 ± 6.84 (range, 165 to 197) cm, while the mean height of the women was 171.60 ± 9.80 (range, 161 to 196) cm. The mean age at menarche of female participants was 14.20 ± 1.31 (range, 12 to 17) years. The mean age for the development of facial hairs in the men was 16.63 ± 1.69 (range, 13 to 22) years (Table 1).

Table 1. Patient demographics.

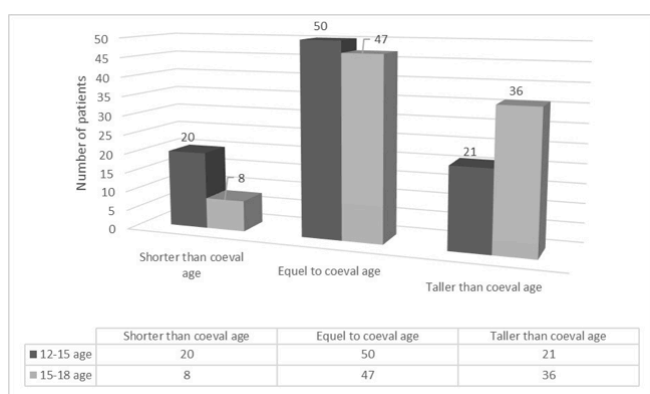
	Male	Female	Total	Turkey Average	
				Male	Female
"n"	81	10	91		
The Mean Age	26.22 ± 7.08	23.30 ± 3.56	25.90 ± 6.83		
The Mean Height	179.8 ± 6.84	171.60 ± 9.80	178.90 ± 7.6	173.3	162.8
The Mean Age at Menarche	-	14.20 ± 1.31	-	-	12.2
The Mean Age of Developing Facial Hairs	16.63 ± 1.69	-	-	14.4	-
Smokers	47	4	51	-	-

All patients were questioned about their height and puberty conditions during the age range of 12 to 15 years and 15 to 18 years (Table 2). Based on these data, 50 (54.9%) reported to have an average height during the age group of 12 to 15, compared to those of the same age group; 21 (23.1%) were tall and 20 (22.0%) were shorter than those of the same age group. The results showed that individuals between the 15 to 18 age group who described themselves as short decreased from 20 (22.0%) to 8 (8.8%), whereas the number of those who

described themselves as tall was found to increase from 21 (23.1%) to 36 (39.6%) (Figure 1). Thirty-nine participants had a sudden increase in height. The peak increase in height of the same age group was found to occur after the age of 16 years. Comparison of the mean age at menarche of women of the study group (14.20 years) with that of Turkish women (12.2 years) [9,10] demonstrated that women of the study group had a statistically delayed onset of menarche ($p < 0.0001$).

Table 2. Patients height status according to age groups.

			15-18 age			Total
			Short	Equal	Tall	
12-15 age	Short	Patients / n	6	10	4	20
		(%) within 12-15 age	30,0	50,0	20,0	100,0
		(%) within 15-18 age	75,0	21,3	11,1	22,0
	Equal	Patients / n	2	32	16	50
		(%) within 12-15 age	4.0	64.0	32.0	100.0
		(%) within 15-18 age	25.0	68.1	44.4	54.9
	Tall	Patients / n	0	5	16	21
		(%) within 12-15 age	0.0	23.8	76.2	100.0
			0.0	10.6	44.4	23.1
Total	Patients / n	8	47	36	91	
	(%) within 12-15 age	8.8	51.6	39.6	100.0	
	(%) within 15-18 age	100.0	100.0	100.0	100.0	

**Figure 1.** Patients height status according to age groups.

Comparison of the mean age of developing facial hairs in men of the study group (16.63 years) with that of Turkish children (14.4 years) [10,11] demonstrated that men of the study group had a statistically later age for the developing facial hairs ($p < 0.0001$).

A total of 51 (56%) individuals were reported to smoke, whereas 40 (44%) individuals had no history of cigarette smoking. Of these individuals, 34 were men and six were women. Irrespective of the cigarette smoking status all participants were re-evaluated. A total of 34 men who did not smoke (Group A) had a mean height of 181.32 ± 6.67 (range, 167 to 197) cm and age of developing facial

hair of 16.44 ± 1.58 (range, 14 to 21) years. On the other hand, six women who did not smoke (Group B) were reported to have a mean height of 175.50 ± 10.61 (range, 168 to 196) cm and a mean age at menarche of 14.50 ± 1.38 (range, 13 to 17) years. Comparison of participants of Group A and Group B with individuals in the normal population demonstrated that the mean age of developing facial hair and the age at menarche was delayed in the study population ($p < 0.0001$).

Discussion

After its first description by Itard in 1803, many researches on PSP have been conducted and many hypotheses have been put forth [1,4,12,13]. It has been shown to be a condition which presents itself as a life-threatening crisis and which is mostly observed in young and tall men [1,4]. This condition has been reported to cause discomfort among participants leading to a change in their lifestyle. Although definite factors have been associated with the mechanism of developing PSP, the most important pathological factors are bulla/bleb formations of the lungs [2]. Thoracic computed tomography (CT) is the most commonly used diagnostic tool during investigation of the etiology of spontaneous pneumothorax. Smit et al. [14] identified bulla or bleb formations in 56% of patients with SP and in 64% of patients with recurrent SP; however, they were unable to identify any pathology in 41% of cases. Many studies reported that the size and location of bullae had no effect on the recurrence rates, although some authors found that CT was essential in identifying pathological features for the prediction of recurrence [15]. Although there are hypotheses on the development of these formations, there is no definite prove to better explain why they develop and why they are mostly found in tall men [13].

Pneumothorax presents with crises. Literature studies demonstrated that 16 to 52% of recurrent cases developed after the first pneumothorax attack, depending on the type of treatment with recurrence within the first 2 to 24 months and a rate of more than half reported within the first four years [4]. The form of treatment of PSP is, however, still a matter of debate. Pleural drainage during the first PSP attack and follow-up in certain selected cases are usually accepted as the optimal approach [2]. Apart from radiologically small-sized (<20%) and clinically asymptomatic and cases with mild symptoms, pneumothorax is a disease condition which necessitates emergency intervention due to its possible fatal complications. As a result, tube thoracostomy (TT) is the mostly commonly referred

treatment method for pneumothorax. However, the guidelines of the British Thoracic Society recommend simple aspiration as the first-line treatment, and suggest that the treatment success rate is similar to TT [16]. On the other hand, in 2001 the American College of Chest Physicians 2001 published that a chest tube or Heimlich valve should be considered as the first-line treatment for PSP patients [17]. In the case of an indication for classical surgical operation for PSP, intrathoracic exploration by videothoracoscopy or thoracotomy would be necessary [G]. In addition, various studies are underway to investigate the method of choice and procedure to prevent recurrence. In a study conducted by Cardillo G et al. [18] to investigate the prevention of the recurrence of pneumothorax, video assisted thoracoscopic surgery (VATS) was implemented with talc poudrage and a recurrence rate of 1.9% was reported. The authors concluded that this rate was significantly higher in cigarette smokers.

In this study, we aimed to move a step further in the etiology of pneumothorax and investigate the causes of this disease. Accordingly, we planned on investigating the growth and development status of mostly young adults. Although participants of our study were about 18-years-old and there was no growth-development chart, we obtained our data using the modified retrospective pubertal-stage assessment form, developed by J Kaiser et al. [8]. In addition to height and weight gain during puberty, changes in the development of secondary sex characteristics, changes in fat and muscle tissue distribution and quantity, and changes in circulation and respiratory system associated with position were reported. This process can be completed with two years in some adolescents, while in others it can take a period of three times more. Menarche is usually the latest physical change observed in girls during puberty. There is a close relationship between menarche and adolescent growth spurt. It is observed after the period, when the growth is fastest. It has been estimated as 12.3 years in the Turkish society [9]. An early age at menarche is known to be associated with short stature during adulthood. The mean age at menarche of 10 women of our study was 14.2 years and this was found to be way more than the known average age at menarche. As observed with menarche in girls, development of hairs in boys was also reported to be around mid-puberty. The adolescent growth spurt curve is observed to peak about two years in women earlier than in men. The short period of adolescent growth spurt forms the peak

height velocity (HtV), which is considered as the fastest time of growth. The peak growth rate in girls during adolescence is 8.5 ± 1.5 cm/years, and peak growth age is 11.3 ± 1.5 years [19], in boys the rate is 10.1 ± 1.6 cm/years, while peak growth age is 13.7 ± 0.7 years [20]. In our study, delayed puberty was reported to be related to menarche and facial hair development which are considered as age markers for mid-puberty. Height velocity is often thought to result in menarche and facial hair development, suggesting that delayed HtV is expected in these patients. Furthermore, results from the history of participants of our study showed that increase in height was delayed due to delayed puberty and that there was late growth, compared to their age group. It is possible that this late growth may possible affect tissue and organ development expected to occur during the normal time interval. This negative interaction may be a factor in the development of pneumothorax, particularly considering the fact that lung development lasts until the age of 18 years.

In conclusion, our study results showed that the patients with pneumothorax had an advanced age at puberty, compared to the normal overall population, and that the pubertal growth spurt occurred within a short period of time. This condition is also suggested to have an effect on the lung maturity and the development of pneumothorax.

Declaration of conflicting interests

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Original Article

Is intercostal nerve protection necessary and safe technique for post-thoracotomy pain?

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ABSTRACT

Background: Our objective in this study was to prospectively evaluate the effects of conventional closure techniques, intracostal suture, and intercostal nerve preservation on postoperative morbidity and long-term pain management.

Materials and Methods: This prospective study was conducted between 2012 and 2015. Three different closure techniques were applied to patients who underwent posterolateral thoracotomy: conventional suture technique, intracostal suture technique, and intracostal suture technique with intercostal nerve preservation. Early postoperative pain level was assessed using a visual analog scale; pain at postoperative six months was assessed with the LANNS pain scale.

Results: Seventy-three male patients (82%) and 16 (18%) female patients were included in the study. Suturing time differed significantly between the groups. At postoperative day 0, 1, and 2, there were significant differences between the groups in pain scores when at rest and while coughing ($p < 0.001$). Complications occurred in 22 patients (24.7%). There were no significant differences in complications between the groups ($p = 0.603$). Chronic pain at postoperative six months was more prevalent in group A compared to groups B and C ($p < 0.05$).

Conclusion: Compared to the conventional technique, the intracostal suture technique with intercostal muscle flap yields better outcomes in terms of early and chronic postoperative pain.

Key Words: pain, chronic pain, thoracotomy, intercostal nerve

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Introduction

Pain is the main problem affecting patients' treatment adherence and daily activities after surgery. Thoracotomy is considered one of the most painful of all surgical procedures [1]. Although there are many studies in the literature on this subject, there is still no clear treatment method [2]. Severe pain in the early postoperative period increases the rate of complications [3]. Early complications include atelectasis, pneumonia, and respiratory failure, while a chronic pain in the late postoperative period impacts patients' daily lives [4,5]. Chronic pain, which is defined as pain that persists for more than six months, occurs at a rate of 67% [2,6].

Our objective in this study was to prospectively assess the effects of conventional closure techniques and intracostal and intercostal nerve preservation on postoperative morbidity and long-term pain management.

Materials and Methods

This prospective study was conducted between April 2012 and November 2015. The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki (Version: B.10.4.ISM.4.06.68.48/184). The preoperative informed consent form was taken from all patients.

All patients in the study underwent posterolateral thoracotomy due to benign and malignant diseases. Of the 126 patients evaluated for the study, 89 patients were included. The patient flow chart for the study is shown in Figure 1.

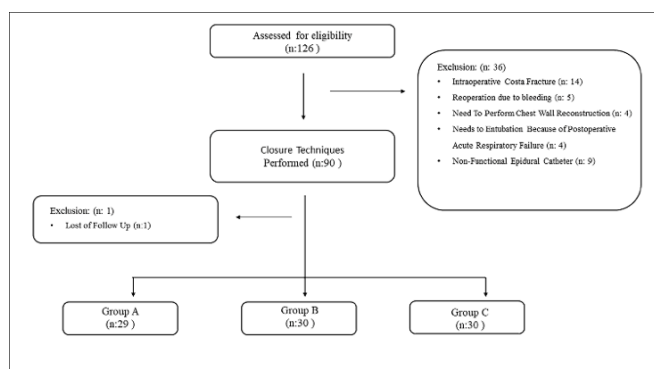


Figure 1. Flow diagram.

Surgeries for malignant disease included lobectomy, pneumonectomy, segmentectomy, and metastasectomy; surgeries for benign disease included lobectomies (bronchiectasis, destroyed lung, and aspergillomas), wedge resection (diagnostic operations), and others (diaphrag-

matic eventration, decortication, paracardiac cyst).

The patients' comorbidities were evaluated in three groups: cardiac problems (past myocardial infarction, heart failure, and arrhythmia), respiratory problems (chronic obstructive pulmonary disease, asthma), and endocrine disorders (diabetes mellitus, goiter). The same surgical team performed all procedures. The patients and observers were blinded to the randomization.

Exclusion criteria for the study included age <18 years; history of previous surgery (thoracotomy); undergoing surgery involving thoracic wall resection; preoperative rib fracture; reoperation due to bleeding; not placed epidural catheter (preoperative epidural catheter wasn't inserted or postoperative catheter displaced early period), needs to intubation because of postoperative acute respiratory failure.

Surgical Technique

For all patients, an epidural catheter was inserted in the area of the fourth or fifth thoracic vertebra under local anesthesia with no intraoperative sedation. With this method, 0.2 g bupivacaine and 500 mg fentanyl were administered postoperatively in 100 cm³ of saline infused at four cm³/s. The epidural catheter was removed on postoperative day 3.

Posterolateral thoracotomy (preserving the serratus anterior muscle) was performed in all procedures. Incisions measuring approximately 20-30 cm were made in the fifth or sixth intercostal space. Ribs were not removed or cut during the procedures.

Three different surgical techniques were used in the study. In group A (conventional suture technique), a Finochietto retractor was placed in the intercostal space during the procedure. At the end of the procedure, two 1/0 polyglactin (Vicryl) sutures were passed through the intercostal muscles to close the intercostal space (Figure 2a). In group B (intracostal suture technique), a Finochietto retractor was placed in the intercostal space during the procedure, as in group A. After the operation; four holes were drilled in the anterior and posterior of the fifth and sixth ribs. In the first ten patients, the holes were made with a hand-held surgical drill. Later, a sternum drill was used to shorten procedure time. Two 1/0 polyglactin (Vicryl) sutures were passed through the holes to close the intercostal space. In group C, the

intracostal muscle (ICM) was partially dissected. The Finochietto retractor was placed in the gap created with this dissection. At the end of the procedure, four holes were drilled in the fifth and sixth ribs, and 1/0 polyglactin (Vicryl) sutures were passed over the ICM to close the intercostal space (Figure 2c). A 28 French thoracic tube was placed in all patients after the procedure.

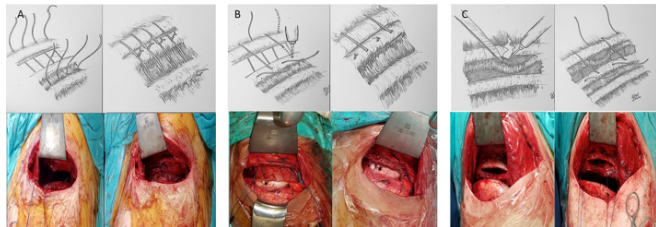


Figure 2. Surgical Closure Techniques (a. Conventional Closure Technique: 1/0 Vicryl sutures are passed through the intercostal space to close the thorax. b. Intracostal Suture Technique: Four holes are drilled in the fifth rib using a hand-held drill or sternum perforator. 1/0 sutures are passed through these holes, and the ribs are closed. c. Intracostal Suture Technique with Intercostal Nerve Preservation: The intercostal nerve is dissected before placing the retractors. The surgical site is closed using the intracostal suture technique).

Postoperative Follow-up

Early postoperative monitoring was done in the intensive care unit. After their general conditions stabilized, the patients were monitored in the inpatient unit. In addition to epidural analgesia, the patients were also administered pethidine 50 mg im 4 times a day on the postoperative day along with diclofenac potassium 2 x 50 mg po and paracetamol 3 x 500 mg po.

In the early postoperative period, the pain was evaluated using a visual analog scale (VAS) in which a score of 0 indicated no pain and a score of 10 indicated the worst pain ever experienced. Pain monitoring was done every 4 hours from postoperative hour 0 to hour 72. Pain levels while at rest and while coughing were assessed.

LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) pain scoring and VAS assessment were repeated at postoperative six months to evaluate chronic neuropathic pain. The LANSS scale is evaluated out of a total of 24 points. Patients with a score of 12 points or less were considered as not having neuropathic pain, while patients with a score higher than 12 points evaluated as having neuropathic pain. VAS assessment at six months was done in

the same way as the previous assessments [7,8].

Postoperative complications that occurred while patients were in the hospital were evaluated. Arrhythmia, pneumonia, atelectasis, and surgical site complications requiring revision were included in the analysis. Lung cancer staging was done according to the IASLC 8th edition staging system [9]. Demographic characteristics, complications, and early and long-term pain were evaluated based on the three different surgical techniques applied.

Statistical Analysis

Continuous variables are presented as a mean $\pm$ standard deviation, and discrete variables are expressed as frequencies. The demographic and clinical characteristics of the patients were tested for normal distribution using the Kolmogorov-Smirnov test. The t-test was used to calculate the means of these variables in the three groups, and the chi-square test was used to compare morbidity between the three groups. Paired samples were analyzed by using Wilcoxon Test. All analyses were performed using SPSS software (version 22; SPSS Inc., Chicago, IL, USA). P values <0.05 were considered significant and p value <0.016 was considered significant between two groups with Bonferroni correction. Power analysis was 0,86.

Results

Of the 89 patients in the study, 73 (82%) were male, and 16 (18%) were female. The mean age was 54.73 ± 12.14 (range 20-78) years, and the mean length of hospital stay was 6.1 ± 4.03 days. Thirty-six (40.4%) of the patients in the study were operated for benign causes and 53 (59.6%) for malignant disease. There were significant differences in length of hospital stay between the patients operated for benign and malignant disease ($p = 0.012$). A comparison of the demographic characteristics of the groups is given in table 1. Intercostal closing time differed significantly between the groups (group A: 3.13 ± 0.85 min., group B: 4.48 ± 1.23 min., group C: 5.59 ± 1.10 min; $p < 0.001$). In benign/malignant diseases subgroup analysis closing time also differed significantly between the groups. $P < 0.001$).

Table 1. Comparison of demographic characteristics of the patients.

Variables	Total n (%)	Grup-A n (%)	Grup-B n (%)	Grup-C n (%)	p-value
Number of Patients	89 (100)	29 (32.6)	30 (33.7)	30 (33.7)	
Sex					
Male	73 (82)	25 (86.2)	24 (80)	24 (80)	0.775
Female	16 (18)	4 (13.8)	6 (20)	6 (20.0)	
Age (Year)		55,79±8,87	55,37±15,41	53,07±11,37	0.431
Comorbidity	24 (27)	11 (37.9)	8 (26.7)	5 (16.7)	0.184
Cardiac Problems	9 (10.1)	3 (10)	2 (6.7)	4 (13.3)	
Respiratory problems	14 (15.7)	6 (20.7)	6 (20)	2 (6.7)	
Endocrinological Problems	8 (9)	4 (13.8)	2 (6.7)	2 (6.7)	
Operation Side					
Right	554 (60.7)	20 (62.5)	14 (51.9)	20 (66.7)	0.502
Left	35 (39.3)	12 (37.5)	13 (48.1)	10 (33.3)	
Histopathology					
Benign	36 (40.4)	13 (44.8)	11 (36.7)	12 (40.0)	0.814
Malignant	53 (59.6)	16 (55.2)	19 (63.3)	18 (60.0)	
Malign Operations					
Lobectomy	37 (69.8)	12 (75)	13 (68.4)	12 (66.7)	0.685
Pneumonectomy	7 (13.2)	2 (12.5)	2 (10.5)	3 (16.7)	
Segmentectomy	4 (7.5)	0	3 (15.8)	1 (5.6)	
Metastasectomy	5 (9.4)	2 (12.5)	1 (5.3)	2 (11.1)	
Benign Operations					
Wedge Resection	25 (69.4)	10 (76.9)	7 (63.6)	8 (66.7)	0.741
lobectomy	4 (11.1)	2 (15.2)	1 (9.1)	1 (8.3)	
Other (Diaphragm Evantration, Decortication, Paracardiac Cyst)	7 (19.4)	1 (7.7)	3 (27.3)	3 (25)	
Hospitalisation (Days)	4±4.03	5.73±4.96	5.0±3.30	4.0±3.79	0.944
Tumor TNM Stage					
1	21 (45.7)	7 (46.7)	8 (53.3)	6 (37.5)	0.861
2	13 (28.3)	4 (26.7)	3 (20)	6 (37.5)	
3	12 (26.1)	4 (26.7)	4 (26.7)	4 (25)	

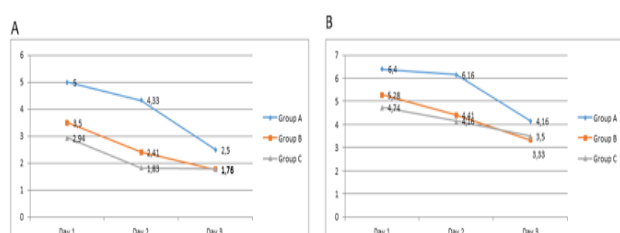
No complications occurred during the intercostal muscle flap procedure. However, during the intracostal suture technique, rib fracture occurred in 2 patients while using the hand-held drill. A sternum perforator was used thereafter to avoid the risk of rib fracture. There was no significant between gender and postoperative pain ($p = 0,217$).

At postoperative day 1, 2, and 3, there were significant differences between the groups in pain scores when at rest and while coughing ($p < 0.001$). With Bonferoni correction, $p < 0,016$ were calculated as a significant value to evaluate between two groups. Resting and

coughing pain scores were significantly higher in group A compared to groups B and C at postoperative day 1, 2 and 3 ($p < 0,001$). Group C showed lower resting and coughing pain scores than group B at postoperative day 2 ($p = 0.012$ and $p = 0.008$). There was no statistical difference between coughing and resting pain scores of group B and C at day 1 ($p = 0.029$ and $p = 0.057$) and day 3 ($p = 0.667$ and $p = 0.700$). When benign and malign patient's pain scores compared separately group A were significantly higher scores. The relationship between surgical procedure and postoperative pain scores are shown in table 2 and figure 3.

Table 2. Postoperative early period pain comparison between groups.

Variables	Grup-A (Mean SD)	Grup-B (Mean SD)	Grup-C (Mean SD)	p Value
Pain Score (VAS)				
Postoperative Day 1 (Rest)	5.00±0.61	3.50±0.91	2.94±1.00	<0.001
Postoperative Day 1(Cough)	6.40±0.68	5.28±1.04	4.74±1.18	<0.001
Postoperative Day 2 (Rest)	4.33±1.36	2.41±0.77	1.83±0.71	<0.001
Postoperative Day 2 (Cough)	6.16±1.34	4.41±0.82	4.16±0.80	<0.001
Postoperative Day 3 (Rest)	2.50±1.25	1.76±0.68	1.78±0.60	0.003
Postoperative Day 3(Cough)	4.16±1.30	3.33±1.04	3.50±0.76	0.002
Benign Group				
Postoperative Day 1 (Rest)	4.96±0.56	3.31±0.75	2.9±1.01	<0.001
Postoperative Day 1(Cough)	6.67±0.83	5.34±0.94	4.71±1.12	0.001
Postoperative Day 2 (Rest)	3.70±1.52	2.54±0.44	1.88±0.72	0.003
Postoperative Day 2 (Cough)	5.74±1.40	4.69±0.42	3.95±0.81	0.002
Postoperative Day 3 (Rest)	2.70±1.08	2.01±0.67	1.59±0.52	0.026
Postoperative Day 3(Cough)	4.51±1.04	4.06±1.33	3.41±0.69	0.029
Malign Group				
Postoperative Day 1 (Rest)	5.02±0.66	3.61±0.99	2.97±1.02	<0.001
Postoperative Day 1(Cough)	6.53±0.56	5.24±1.11	4.76±1.24	<0.001
Postoperative Day 2 (Rest)	4.22±1.22	2.44±0.92	1.94±0.72	<0.001
Postoperative Day 2 (Cough)	6.38±1.26	4.43±0.99	3.83±0.81	<0.001
Postoperative Day 3 (Rest)	2.75±1.41	1.61±0.65	1.91±0.63	0.022
Postoperative Day 3(Cough)	4.66±1.52	3.34±0.75	3.75±0.80	0.020

**Figure 3.** A. Graph of mean pain scores at rest B. Graph of mean pain scores at at cough.

Totally 26 complications were occurred in 22 pa-

tients (24.7%). The complication rate was higher in group A (31.9%) compared to groups B (20%) and C (23.3%), but the difference was nonsignificant ($p = 0.603$). Atelectasis was more common in group A than in the other groups but it was not significant when compare with the groups ($p = 0.027$). No statistical difference was found when the complications of patients with the malignant and benign disease were compared based on closure technique ($p = 0.690$ and $p = 0.487$) (Table 3). To evaluate secretion retention fiberoptic bronchoscopy was performed in patients with atelectasis.

Table 3. Postoperative complication comparison between groups

Variables	Total n (%)	Grup-A n (%)	Grup-B n (%)	Grup-C n (%)	p-value
Complications					
Arrhythmia	12 (13.5)	3 (10.3)	5 (16.7)	4 (13.3)	0.776
Pneumonia	3 (3.4)	1 (3.4)	0	2 (6.7)	0.359
Atelectasis	8 (9.0)	6 (20.7)	1 (3.3)	1 (3.3)	0.027
Wound Infection	3 (3.4)	1 (3.4)	1 (3.3)	1 (3.3)	1
Malign patients Complications	17 (32.1)	6 (37.5)	5 (26.3)	6 (33.3)	0.772
Benign patients Complications	5 (13.9)	3 (23.1)	1 (9.1)	1 (8.3)	0.482

Although no statistically significant difference was observed in VAS scores at postoperative 6 months, there was a significant difference in LANSS scores between patients in group A and patients in groups B and C. By

Bonferroni correction, Group A found significantly higher rates of patients with LANSS scores > 12 than two other groups ($p < 0.001$). Between group B and C there was not any significant difference ($p = 0.317$).

That showed LANSS score difference was caused by group A. There were no superiority between intracostal suture technique and intracostal muscles flap technique in LANSS score. A statistically significant difference was found between LANSS scores when the closure techniques were compared among patients with benign and malignant diseases (Table 4). At postoperative six

months, 28.1% of the patients (n = 25) required intermittent treatment with nonsteroidal anti-inflammatory drugs. Twenty-nine patients (32.6%) developed post-thoracotomy pain syndrome (PTPS). There was no statistically significant sex difference in terms of prevalence of 6-month pain (22 males [30.1%] vs. 7 females [43.8%]; $p = 0.293$).

Tablo 4. Comparison of the 6-month pain score between the groups

Variables	Grup-A n (%)	Grup-B n (%)	Grup-C n (%)	p Value
VAS	2,48±2,02	1,63±1,65	1,93±1,81	0.220
LANSS				
Score <12	11 (37.9)	26 (86.7)	23 (76.7)	<0.001
Score >12	18 (62.1)	4 (13.3)	7 (23.3)	
Malign LANSS				
Score <12	7 (43.8)	17 (89.5)	13 (72.2)	0.013
Score >12	9 (56.3)	2 (10.5)	5 (27.8)	
Benign LANSS				
Score <12	4 (30.8)	9 (81.8)	10 (83.3)	0.008
Score >12	9 (69.2)	2 (18.8)	2 (16.7)	

Discussion

Although there are many studies in the literature about chronic pain, our understanding of the phenomenon remains limited. Despite the development of many new drugs and techniques for relieving pain, it continues to be one of the biggest problems facing medicine today [8,9]. Systemic opioids, nonsteroidal anti-inflammatory drugs, epidural analgesics, and techniques such as intrapleural and intercostal nerve blocks are used to relieve post-thoracotomy pain. However, none of these techniques can adequately control pain in some cases.

In the late postoperative period, some patients have complaints of burning, numbness, and stinging, which characterize neurogenic pain. This chronic pain is referred to as PTPS or chronic post-thoracotomy pain (CPTP). PTPS develops at a rate of 30-50% after thoracotomy [10–12]. However, due to the lack of standard criteria for PTPS, the reported incidence ranges considerably. The pain persists for a period of 2 months to 5 years on average. According to the definition by the International Association for the Study of Pain, chronic post-thoracotomy pain persists or recurs for two months or longer after surgery [13], while Cerfolio [14], Kalso [15], and Katz [6] state this period as six months. In our study, we evaluated patients' pain levels at postoperative six months to assess the effect of different surgical

closure techniques on rates of chronic pain, and we determined that 32.6% of the patients have PTPS. Compared to the conventional suture technique, intercostal and intracostal nerve preservation techniques significantly reduced chronic pain.

PTPS is thought to be the result of injury to the intercostal nerves, which transmit pain signals from the chest wall and costal pleura [16]. Pain can arise due to incision shape, muscle separation, intercostal nerve damage, or tube location. The most important of these factors is intercostal nerve damage [2,17,18]. Rib retraction is believed to be a common cause of this damage.

Age, sex, previous surgical interventions, genetic predisposition, and psychosocial factors are thought to influence chronic pain [19]. To date, however, no studies have shown that age and sex are risk factors for chronic post-thoracotomy pain [20]. Similarly, we also detected no correlation between demographic characteristics and pain.

In 2003, Cerfolio [3] showed in a study of 280 patients that the intracostal suture technique significantly reduced pain in the first three months postoperatively compared to the pericostal suture technique ($p < 0.001$). In a 2005 study, he evaluated ICM cut with ICM flap for preventing nerve damage due to retraction. The patients

with ICM flap had significantly less pain at 12 weeks ($p = 0.002$) [21]. For this reason, we used ICM flaps instead of ICM cut in our study. Bayram et al. [15] compared two intracostal suture techniques, one of which avoided compressing the intercostal nerve, and showed that patients without intercostal nerve compression had less pain at rest and during coughing. In our study, we evaluated the long-term results of a pericostal sutures and intracostal sutures with and without ICM flap. In terms of early postoperative pain, we achieved better results in patients without intercostal nerve compression compared to the conventional method ($p < 0.001$). Although there was no difference between the intracostal suture techniques with and without nerve compression in terms of pain at postoperative six months, both techniques were superior to the conventional pericostal suture method.

Cerfolio [3] reported that pain is the most important independent factor increasing postoperative morbidity and mortality. In a prospective study by Wu et al. [15] comparing intracostal suture and ICM flap techniques, no difference was observed in terms of early complications (arrhythmia and atelectasis). The authors also reported no difference in postoperative pain scores at rest and while coughing. However, oxycodone use was significantly lower in the ICM flap group during postoperative days 4–7. They detected no significant difference in general complications based on suture technique.

In our study, we noted a significant difference in operative time between the suture technique groups. This was due to the use of a hand-held drill when initially practicing the intracostal suture technique. However, because it extended the procedure time, a sternum perforator was used in subsequent cases. This technique enables holes to be drilled in the ribs rapidly. In addition, using a sternum perforator eliminates the risk of rib fracture and a major injury to the lung parenchyma and heart which can occur when using a drill. Although the intracostal suture procedures result in longer operative times, we do not consider the difference great enough to cause an increased anesthesia risk. Therefore, we believe these techniques are feasible and beneficial for reducing pain in the long term.

Study Limitations

Despite being a prospective study, evaluating patients with malignant and benign pathologies together result-

ed in heterogeneity in the study sample. There was also heterogeneity regarding disease stage within the malignant disease group. Furthermore, the patients' postoperative oncological treatments were not considered when evaluating the patients' pain responses. We have not evaluated analgesic strategies which were used after surgery. Another limitation of the study is the wide age distribution of the patients.

As a conclusion, the intracostal suture technique with ICM flap resulted in less early postoperative pain and chronic pain compared to the conventional technique. Reduced pain, especially in patients with limited respiratory reserve, prevents atelectasis. Our findings indicate that chronic pain can be reduced by preventing intercostal nerve damage. Intracostal suture technique and ICM flap technique have advantages over conventional techniques. However, there are no long-term clinical differences between each other. For this reason, we recommend that these methods be preferred to routine procedures instead of conventional techniques.

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Case Report

Primary sarcomas of the lung: report of five cases and review of the literature

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ABSTRACT

Primary pulmonary sarcomas of the lung are rare tumors with a low incidence. We reviewed the literature and analyzed 5 patients retrospectively. All clinical datas and therapeutic protocols were recorded. The required surgical procedure was lobectomy in 4 patients and diagnostic bronchoscopy and mediastinoscopy in one patient. At histological examination; 2 carcinosarcoma, 1 undifferentiated pleomorphic sarcoma, 1 leiomyosarcoma and 1 synovial sarcoma diagnosed. Primary sarcomas of the lung cannot be differentiated from more common tumors of the lung tumors clinically. Early diagnosis and complete surgical resection is critical for prognosis.

Key Words: carcinosarcoma, leiomyosarcoma, sarcoma, synovial sarcoma

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Introduction

Primary pulmonary sarcomas of the lung are very rare malignant tumors of the lung [1]. The incidence of this tumor is very low. They account less than 0.5% of all lung tumors and we have very limited knowledge about the clinical behaviour and futures when compared to the other lung tumors [2].

Differential diagnosis is critical for treatment. Additional histopathological and immunohistochemistry (IHC) examination could be required for a definitive diagnosis [1,2].

Surgical management consists radical resection with pathological free margins is still the gold standard for the treatment. Postoperatively chemotherapy and/or radiotherapy is often advised. However, a standard therapy protocol is not clear for the patients having primary pulmonary sarcoma of the lung [1,2].

We retrospectively analyzed 5 patients with primary sarcoma of the lung managed in our department during a 5-year-period in a single institution and reviewed the

international medical literature.

Cases Reports

Records of 5 patients diagnosed with primary pulmonary sarcoma of the lung between 2014 and 2018 in our department were reviewed. Demographic data, past medical and familial history, and all clinical symptoms were noted. Chest films, computed tomography (CT) and positron-emission tomography (PET) scans were examined for the tumor location, tumor size, invasion, metastasis and maximum standard uptake value (SUV-max). Therapeutic protocols of surgery, chemotherapy and/or radiotherapy were also recorded. Pathological slides were examined by the same pathologist, experienced in the lung tumors. Electron microscopy and IHC were also performed. The mean diameter of the tumor, invasion (lymph nodes, pleura, diaphragm, muscle, chest wall, etc.), surgical margins and pathologic diagnosis were recorded. Follow-up period of the patients after surgery were listed. Detailed clinical and evaluative features of all patients are given at table 1.

Table 1. Detailed clinical and evolutive features of patients

Patient Number	Sex	Age	Symptoms	Size of Tumor [cm]	Location	Treatment	Histopathological Diagnosis	Local Invasion	Follow-up [m]	Additional Therapy
1	M	58	Chest pain	7.5	Right Upper Lobe	Lobectomy	Carcinosarcoma	No	52-alive	CRT
2	M	65	Asymptomatic	2.1	Left Upper Lobe	Lobectomy	Undifferentiated Pleomorphic Sarcoma	No	33-alive	No
3	F	52	Dyspnea Haemoptysis	4	Left Lower Lobe	Lobectomy	Leiomyosarcoma	Diaphragm Pleura	19-died	CRT
4	M	70	Hoarseness Chest pain	4.1	Left Upper Lobe	Bronchoscopy Mediastinoscopy	Carcinosarcoma	Lymph nodes [N2-N3]	2-died	CRT
5	F	51	Chest pain	6.9	Left Lower Lobe	Lobectomy	Synovial sarcoma	Diaphragm Muscle Pleura	1-alive	CRT

CRT: Chemotherapy and Radiotherapy

Case 1

A 58-year-old man with severe right lateral chest pain was admitted to our clinic. He was a heavy smoker and his medical history is nonspecific. Blood chemistry and hematological examinations were normal. A chest X-ray and CT showed a 7.5 cm solid lesion at right upper lobe. At PET/CT scan, SUV-max of the mass was 9.2

g/ml and there were no lymph node invasion or distant metastasis. The patient was operated and right upper lobectomy and mediastinal lymph node dissection was performed. At pathological and IHC examination carcinosarcoma diagnosed, the mean diameter of tumor was 7.5x7x5.5 cm, and there were no lymph node or pleura invasion with free margins. After the surgical procedure

patient has received chemotherapy and radiotherapy. He is still alive and follow up from 52 months without recurrence and metastasis.

Case 2

A 65-year-old man previously healthy man admitted to our clinic for a 2 cm lesion of left upper lob. The patient was asymptomatic and the mass was diagnosed incidentally during a check up. CT and PET/CT revealed a 2 cm peripheral cavitory lesion at the left upper lobe (SUV-max 11 g/ml). A left upper lobectomy was performed, at pathological and IHC examination, undifferentiated pleomorphic sarcoma was diagnosed. Diameter of tumor was 2.1 cm and there were no lymph node invasion. Chemotherapy and/or radiotherapy was not performed after the surgery. The patient is free of disease and followed up for 33 months.

Case 3

A 52-year-old women presented with dyspnea and hemoptysis for 2 months. She also had a history of hyperthyroidism and underwent a radioactive iodine treatment 7 years previously. She is also a heavy smoker. CT and PET/CT showed a 4 cm lesion at the left lower lobe (SUV-max 9.2 g/ml) with a suspicious diaphragma invasion. Left lower lobectomy performed with partial diaphragma resection. Pathological specimen was leiomyosarcoma grade-1, with pleura invasion, lymph nodes and diaphragmatic margins were tumor negative. Patient had received chemotherapy and radiotherapy, but she died after 19 months due to the progression of the tumor.

Case 4

A 70-year-old man admitted to our clinic with hoarseness and chest pain. He was a heavy smoker and had a history of asbestosis. He had a family history of lung cancer. CT and PET/CT scans revealed a lesion at right vocal cord (SUV-max 7.1 g/ml), left intraclavicular and mediastinal multiple lymph nodes (SUV-max 14.5- 22.3 mg/dl) and a 4.1 cm solid lesion of left upper lobe (SUV-max 18.9 g/ml). Endobronchial ultrasound could not be performed because the patient did not accept any approach with local anesthesia or sedation. Bronchoscopy was performed under general anesthesia and carcinosarcoma was diagnosed. He received chemotherapy and radiotherapy but died 2 months later with progression of the tumor.

Case 5

A 51-year-old women presented with a left lateral chest pain. She had a past medical history of tumor resection from her leg and received radiotherapy 30 years previously with the diagnosis of fibrosarcoma. She also had a family history of liver carcinoma, larynx carcinoma and lymphoma. At CT and PET/CT scans a 6.9x4.7 cm lesion (SUV-max 9mg/dl) at the left lower lobe was found (Figure 1). Left lower lobectomy with partial diaphragma resection was performed. Pathological specimen was synovial sarcoma with pleural and muscular invasion. There were no lymph node invasion and free margins of tumor. She was operated 1 month ago, chemotherapy and radiotherapy will be planned.

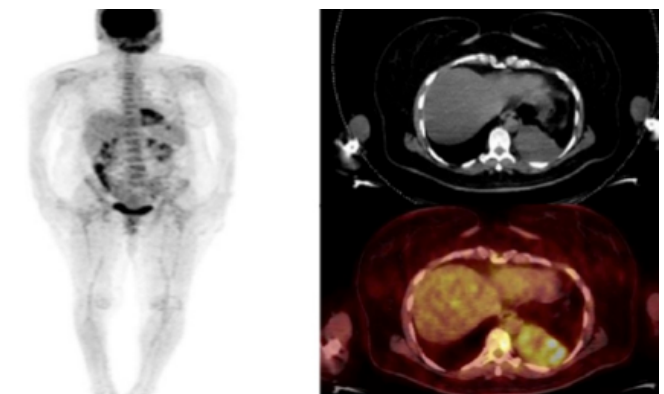


Figure 1. CT and PET scans revealed a 6.9x4.7 cm solid lesion (SUV-max 9mg/dl) at the left lower lobe.

Discussion

Sarcomas are uncommon primary malignant tumors of the lung and account for less than 0.5% of the cancers of the lung so we have only a little experience about these tumors [2]. Cameron found only nine patients in a series of 6000 primary lung neoplasms (0.15%) in 1975, and Miller found only 30 out of 10134 lung neoplasms (0.3%) [2,3].

Detailed IHC studies began after 1985 and then allowed a better classification of sarcomas, based on the predominant histological pattern of growth and cytological composition [1]. In the lung, primitive mesenchymal cells may arise from the stromal elements of the parenchyma like bronchial or vascular wall. They usually expand towards the parenchyma [4].

Parenchymal and endobronchial sarcomas include; fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma,

hemangiopericytoma, osteosarcoma, myxosarcoma, spindle cell sarcoma, angiosarcoma, malignant fibrous histiocytoma, malignant schwannoma, malignant mesenchymoma, undifferentiated sarcoma, pulmonary blastoma, neurogenic sarcoma, chondrosarcoma, synovial sarcoma and liposarcoma [1]. The most common types are leiomyosarcomas, fibrosarcomas and hemangiopericytomas. In this study, carcinosarcoma was the most common type.

Incidence of primary pulmonary sarcomas are equal in males and females, and can occur at any age with a range of 4 to 83 years showing a slight predominance at middle ages [1,2]. In this study, there are 3 male and 2 female patients between 51-70 years age.

Most of the patients are asymptomatic and the mass is incidentally diagnosed [1]. Only one patient in this series is asymptomatic who had a small tumor size (2.1 cm). Other patients having tumors of 4 to 7.5 cm had symptoms such as dyspnea, hoarseness, hemoptysis and chest pain. Fever, fatigue, anorexia and weight loss are later symptoms. Presenting symptoms are similar to those of bronchogenic carcinoma. On radiographs the tumor is usually presented as a large peripheral well-circumscribed solitary mass and vary in diameter from 1 to 15 cm. In this series, it varied from 2.1 to 7.5 cm [1].

Thorax CT scan is an important diagnostic tool as the tumor often invades pleura, pericardium, vessels and chest wall [5]. Two patients in this series had diaphragmatic invasion, they were diagnosed as leiomyosarcoma and synovial sarcoma. The tumors were 4 and 6.9 cm, and left lower lobectomy performed for both of them with an additional partial diaphragma resection.

Differential diagnosis of primary lung sarcoma is critical for the treatment. The gross presentation of these tumors does not differ significantly from the more common tumors of the lung and from the metastatic sarcomas. Detailed clinical history, presence of past soft tissue neoplasms, previous radiation exposure is critical for distinction of these tumors. The tumors should be diagnosed with histological methods and molecular techniques immediately after other alternative diagnosis were excluded. Small biopsy samples might be very challenging so wide resection materials are better for di-

agnosis. Treatment and prognosis differs from the other soft tissue sarcomas and bronchogenic carcinomas [2,6].

Complete surgical resection with lobectomy, pneumonectomy or segmentectomy with pathological free margins is the best option for treatment [4]. We performed 4 lobectomy in 5 patients. In most of the series in the literature, a high percentage of large tumors were reported and resections are extended to the chest wall, diaphragm, superior vena cava or auricle. Two patients in this series diaphragmatic resection was performed. Porte reported extended resections at 6 out of 18 patients and Bacha at 6 out of 19 patients. [4]. Mediastinal lymph node dissection was performed in all patients. Primary lung sarcomas rarely disseminate to lymph nodes. Regnard et al. found N2 involvement in 2 out of 20, and N1 involvement in three patients [4]. Mediastinal lymph node dissection were routinely performed at our clinic and we did not see any lymph node invasion except the patient that was diagnosed at the terminal stage.

Positive resection margins are related poor prognosis. Bacha reported 6 patients out of 20 had positive resection margins [4]. Large tumor size is also a poor prognostic factor. According to Nascimento et al. 5 cm and Jansen et al. 4 cm tumor size indicated a poor prognosis [4]. In the series of MacCormack and Martini, and Burt and Zakowski a tumor diameter of 5 cm or less is related better prognosis. However Regnard and Bacha did not find that tumor size a prognostic factor [4]. Additional chemotherapy and/or radiotherapy is a piece of advice of treatment but the efficacy of them is still poor because they do not have standart protocols and they need further studies [4].

Carcinosarcoma of lung is a rare tumor and its incidence is 0.1 to 0.4% of all lung malignancies [7]. In the literature, pulmonary carcinosarcoma was first described in 1908, that a complex tumor for diagnosis [8]. The World Health Organization (WHO) classification of 2015 identified carcinosarcoma as a subtype of sarcomatoid carcinoma and defined as malignant neoplasm composed of both malignant epithelial and mesenchymal elements [1,9]. The most frequent epithelial component is squamous carcinoma and sarcomatous component is rhabdomyosarcoma. Our two patients also had the two components just like the literature [8,10]. In the

literature, fewer than 20 cases are reported until 1995 [11-14]. Ishida et al. [15] reported 5 cases, Kimino et al. reported a case, Grahmann et al, Berho et al, Zehani et al. and Wick et al reported 3 cases of each [1,16]. Xu et al. [17] reported 48 cases and this is one of the largest series of the literature. They usually seen an average age of 60-year-old males of heavy smokers [8]. We have two male patients of 58 and 70 year ages and both of them were heavy smokers. Carcinosarcomas usually grow slowly and clinical symptoms depend on the location and size of the tumor. Complete resection of the tumor is the essential treatment. The role of chemotherapy is still very poor. Liang et al. [18] and Raveglia et al. [19] both reported failures of patients' survival. [7] The five year survival rate varies between 6-49.4% [1,8]. According to Xu et al. [17] the 1-3 and 5-year survival rate was 77.1%, 49.5% and 22.7%. Our one patient is still alive for 52 months and free of disease, the other patient died within two months, but he was in the terminal level when diagnosed.

Undifferentiated pleomorphic sarcoma, redefined by Fletcher in 2002, after the development of IHC techniques they examined more carefully. Before IHC, they diagnosed the cases as malignant fibrous histiocytoma [1,20]. They are rare tumors, 0.1-0.4% of all lung malignancies [21]. They are high grade sarcomas and show progressive and rapid growth. Sarcomas have an aggressive clinical course, metastasis and recurrence incidence is high [22]. Surgical resection is gold standart for treatment, and we performed lobectomy to our patient. Palliative chemotherapy or radiotherapy may be used. Our patient had a small tumor of 2.1 cm diamater and there were no lymph node invasion, surgical margins were free of tumor, so he did not take chemoradiotherapy. 5-year survival of undifferentiated pleomorphic sarcoma is approximately 50% [22]. During the follow up of 33 months he had no metastasis or recurrence. Xu reported a 59-year-old woman with symptomatic right atrium metastasis of an undifferentiated pleomorphic sarcoma of lung. She diagnosed as stage 4 lung cancer of left upper lobe and she has undergone chemoradiotherapy. After a followed up of 4 years, she had been operated for atrial metastasis and follow up for two months without recurrence [22]. Goncalves et al [23] reported

a 66-year-old man, diagnosed as undifferentiated pleomorphic sarcoma at the right upper lobe, he was treated with endobronchial tumor debulking by laser therapy and radiotherapy and survived over 11 years. Abreu et al [21] also reported a 74-year-old patient with a 7 cm lesion at right hemithorax.

Leiomyosarcoma, rarely arises in the lung, differentiated from smooth muscle and originated from pulmonary artery, bronchus or pulmonary parenchyma [6,24,25]. The tumor accounts 0.5% of the malignant tumors of lung [24]. Age range is wide, 5 to 76 years and our patient was 52-year-old. Most of the patients were asymptomatic and if symptom is present they are usually chest pain, hemoptysis and cough. The tumor can present with Pancoast tumor [25]. Our patient referred to our clinic with dyspnea and hemoptysis. The radiological features are nonspecific, tumor sizes varies from 1.7 to 10 cm diameter. Our patient had a 4 cm lesion at the left lower lobe with suspicious diaphragma invasion. [26] The earliest case was reported in 1907 by Davidsohn [24,27]. Agnos and Starkey recorded 18 cases in 1958, Dyson and Tretalance reported 26 cases in 1964 [28] and Guccion et al and Nascimento et al have reported 41 cases [1]. Porte et al [4] reported 2 cases, Janssen et al [27] 8 cases and Mastroianni et al [2] 7 cases. Surgical resection is the best treatment option and lobectomy was performed with diaphragma resection. The surgical margins and lymph nodes were free of the tumor in our case. The tumor can make distance metastasis but it's uncommon, Young et al reported the thyroid metastasis after lobectomy [24,29]. If an early and complete resection was performed, 5-year survival rate is reported as 50%. However the prognosis is usually poor, only a few patients lived 15 to 20 years, our patient died after 19 months from the progression of the tumor [24].

Synovial sarcoma, is defined by the 2004 WHO classification and it is a mesenchymal spindle cell tumor which variably displays areas of cellular differentiation [6,30,31]. Cytogenetic studies showed a translocation over chromosome 18 [32]. Histopathologically its divided as; biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated types. Our patient was diagnosed as biphasic synovial sarcoma [32,33]. It is a rare tumor and only 0.1% of all resected malignant

lung tumors, also 5-10% of all human soft tissue sarcomas [34-36]. They usually occurs in extremity, especially around the knee [37-39]. Its range is 3 to 84 years of age and slightly more frequent in woman [34]. The usual symptom is dyspnea, cough, chest pain, and hemoptysis similar to the other tumors of the lung. The tumor was not encapsulated in at least 75% of reported cases just like our patient [6]. Niwa et al [40] reported a case that exhibits a polypoid endobronchial growth. Tumor size ranges between 0.6 to 17 cm and in our case it was 6.9 cm. Primary resection is the best treatment and lobectomy was performed in our patient. These tumors may infiltrate pleura, chest wall and mediastinum. Our patient had an invasion of diaphragm, pleura and muscular layer. Distant metastasis can also be seen. Ezzine et al reported an intracardiac metastasis, Ogino et al. brain metastasis and Seyhan et al vertebra metastasis [35,36,41]. Zeren et al reported 25 similar cases, Essary et al reported 12 cases [1,42]. Jiang et al reported approximately 73 cases reported in the literature since 2008, Nakano et al. reported 60 cases since 2010 and Ozdil et al. reported 90 cases since 2018 [31,33,38,39]. The patient is in the first month of follow up, chemotherapy and radiotherapy is planned. The tumor is chemosensitive, adriamycin alone or in combination with ifosfamide remains the standard protocol. Radiotherapy is used for achieving excellent local control after surgery [37]. Metastasis and recurrence rates are low so 10-year survival can be seen, survival rates are between 1 month to 19 years [38]. High grade metastatic tumors are with poor prognosis and 75% dead within two years. Poor prognostic factors are, tumor size over 5 cm, male sex, greater than 20 years of age, extensive tumor necrosis, neurovascular invasion and large number of mitotic figures [30]. Generally 5 year survival rate is 30-50% [30,37]. Spontaneous regression of tumor without a treatment is also very rare and occur in 1 in 60,000 to 100,000 cases of all malignancies [43]. Tsunetsuka et al reported a 38-year-old patient with spontaneous regression of tumor after transbronchial biopsy, 2 months after biopsy lobectomy performed to the patient but there were no tumor at the pathological examination [43].

In conclusion primary sarcomas of the lung are very rare and aggressive malignancies. Clinically they cannot

be differentiated from more common tumors of the lung and metastatic sarcomatous tumors. Early diagnosis and complete surgical resection before the tumor become larger and metastatic is critical for prognosis. Efficacy of chemotherapy and/or radiotherapy is still not clear so a multidisciplinary approach may be useful. Primary sarcomas of the lung must always be remembered for the differential diagnosis of the other tumors and a complete resection should be performed immediately for better prognosis.

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Case Report

A rare lung tumor: pulmonary carcinosarcoma

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ABSTRACT

Pulmonary sarcomatoid carcinoma is an extremely rare malignant lung tumor with an unfavorable prognosis, which shows carcinomatous and sarcomatous components. We present a case of 78-year-old patient with a middle lobe tumor who underwent a bronchial sleeve middle lobectomy. The tumor was a carcinosarcoma with squamous cell carcinoma and rhabdomyosarcoma components histologically. We tried to emphasize this extreme lung tumor and its clinicopathological features.

Key Words: pulmonary carcinosarcoma, surgery, resection

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Introduction

Pulmonary sarcomatoid carcinoma is an extremely rare malignant lung tumor, accounting for less than 1% of all lung tumors. It is a biphasic lung tumor with an unfavorable prognosis, which shows carcinomatous and sarcomatous components. The World Health Organization (WHO) defined five subtypes of pulmonary sarcomatoid carcinomas such as giant cell, spindle cell, and pleomorphic carcinoma, carcinosarcoma and pulmonary blastoma [1].

We present a case of 78-year-old patient with a middle lobe tumor who underwent a bronchial sleeve middle lobectomy. The tumor was a carcinosarcoma with squamous cell carcinoma and rhabdomyosarcoma components histologically. We tried to emphasize this extreme lung tumor and its clinicopathological features.

Case report

Our patient was a 78-year-old asymptomatic male who had undergone a coronary bypass surgery and was found to have a lung mass during follow-ups. He also had hypertension and a right nephrectomy for benign renal disease. He has a history of 25 pack-year smoking and asbestos exposure. A chest X-ray showed a right hilar mass appearance which was confirmed with computerized tomography. The tumor was located at the medial segment of the middle lobe at the hilar region, measuring 65x32 mm in diameter and obstructed the middle lobe bronchus (Figure 1). A whole body PET/CT showed a tumor in the middle lobe with a standard uptake value of 18 without any involvement of mediastinal lymph nodes (Figure 2).

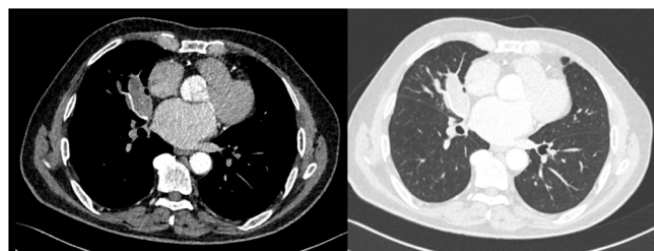


Figure 1. Thorax computed tomography showing the tumor located in the middle lobe.

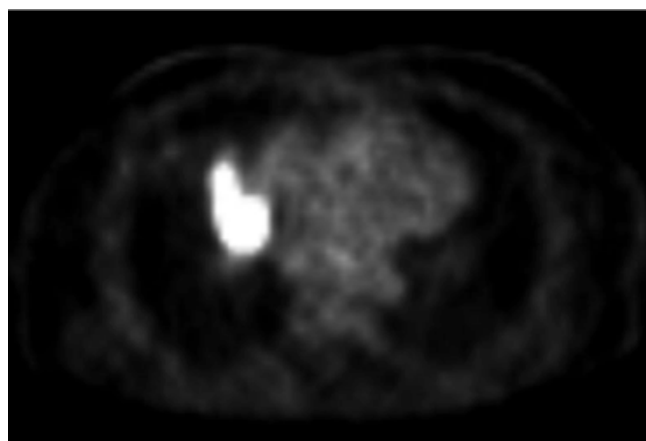


Figure 2. Positron Emission Tomography showing the hilar tumor with a high uptake value (SUVmax: 18).

He also had two benign cystic lesions in the liver without any uptake. Cranial magnetic resonance imaging showed no metastasis. Bronchoscopy showed an endobronchial tumor at the orifice of middle lobe bronchus extending into the intermediate bronchus. Biopsy revealed necrotic tissue with a focal immature mesenchymal element consistent with either a pulmonary blastoma or other sarcomatoid carcinoma variants. No definite diagnosis could be given due to the limited tissue. The patient had no metastasis of mediastinal lymph nodes on mediastinoscopy. He underwent a right posterolateral thoracotomy and a bronchial sleeve middle lobectomy with mediastinal lymph node dissection. Histological findings showed a biphasic tumor composed mostly of spindle cell tumor with rhabdoid features. Epithelial component was focally present. Immunohistochemical examination supported the biphasic nature of the tumor. Sarcomatoid component was positive for desmin and myogenin. Epithelial component was positive for pancytokeratin, p63 and EMA (focal) (Figures 3,4).

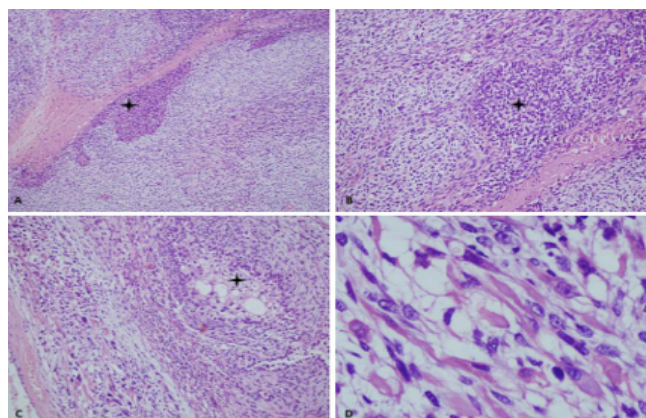


Figure 3. Tumor composed of both sarcomatous and epithelial (asterisks) components (A-C). Sarcomatous component showing rhabdomyomatous differentiation with cross-striations (D) (Hematoxylin-Eosin).

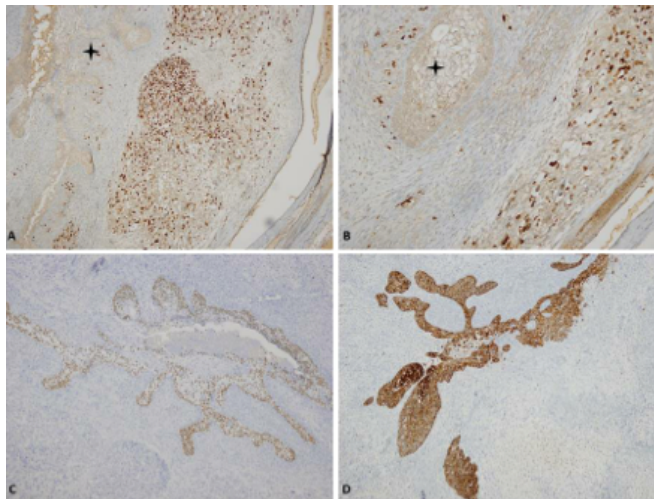


Figure 4. Immunohistochemistry shows positive immune reactivity for Myogenin only in sarcomatous component (A-B). Epithelial component shows p63 (C) and Pancytokeratin (D) positivity.

The tumor was negative to TTF-1, SMA, CD34 and S100. Histologic diagnosis was a carcinosarcoma. A total of 80% of the tumor histologically showed features of a rhabdomyosarcoma, whereas the remainder of 20% was a squamous cell carcinoma. The patient did not receive any adjuvant chemotherapy. He is doing well at postoperative six months.

Discussion

The most recent WHO classification of lung tumors classifies the pulmonary sarcomatoid carcinomas variants into five groups such as pleomorphic, spindle cell and giant cell carcinoma, pulmonary blastoma and carcinosarcoma [1]. Pleomorphic carcinoma is a poorly differentiated carcinoma containing at least 10% spindle and/or giant cells along with a non-small cell carcinoma variant, mostly squamous cell carcinoma or an adenocarcinoma. Spindle cell carcinoma consists of only spindle cells and is identical to the spindle cell component of pleomorphic carcinoma. Giant cell carcinoma is composed entirely of highly pleomorphic giant cells. Pulmonary blastoma is a biphasic tumor with a primitive epithelial component that may resemble a well-differentiated fetal adenocarcinoma and primitive mesenchymal stroma. The last variant, pulmonary carcinosarcoma is defined as a malignant tumor with a histologically biphasic mixture of conventional non-small cell carcinoma and true sarcoma containing differentiated sarcomatous elements such as malignant cartilage, bone, or skeletal muscle [1]. The carcinomatous

component in a carcinosarcoma is most often a squamous cell carcinoma as in our case, followed in frequency by adenocarcinoma and large cell carcinoma. The sarcomatous component is often poorly differentiated spindle cell carcinoma, which shows areas of more specific sarcomatous differentiation, most often rhabdomyosarcoma as seen in our case, followed by osteosarcoma or chondrosarcoma comprising combinations of these components. Tumor genotyping in pulmonary carcinosarcomas shows identical mutations in both the carcinomatous and sarcomatous components, which supports the hypothesis that both components originate from a single clone [1,2]. This finding is an evidence that sarcomatoid carcinomas represent malignant “epithelial” neoplasms that have undergone divergent connective tissue differentiation and they are not “collision” tumors [1].

Pulmonary carcinosarcomas are poorly differentiated lung tumors mostly occurring in heavy smokers with an asbestos exposure at a mean age of 65 years. Patients have a male predominance with a rate of seven [3]. Similarly, our patient is a 78-year-old ex-heavy smoker with a history of asbestos exposure.

Cough, fever and hemoptysis are the most common symptoms. Chest pain, fever and malaise may also occur. A very rare symptom such as pulmonary osteoarthropathy has also been described [4]. Patients with peripheral tumors may be asymptomatic. On the other hand, tumors are often located centrally with an endobronchial extension at a rate of 62%. They are frequently slow growing tumors and more likely to grow into the bronchi without any infiltration. They may show extensive invasion to the surrounding lung parenchyma. Tumor location is mostly upper lobes and the greatest dimension of the tumors has an average of 7 cm. Preoperative diagnosis with either endobronchial or transthoracic biopsy may be difficult if the biopsy specimens show only one component [5]. However, endobronchial biopsy showed biphasic histological features in our patient. Metastases to the regional lymph nodes and distant organs, particularly to the brain are common. Our patient has a big central tumor obstructing the middle lobe bronchus, however he has neither regional nor distant metastasis.

Surgery is the choice of treatment for pulmonary carcinosarcomas, however they are highly aggressive tu-

mors with poor outcomes. Tumours with endobronchial localization have comparably better prognosis because peripheral tumors tend to metastasize early and widely. The surgical outcome is not favorable with a five-year survival rate ranging from 12 to 49% [3,6,7]. Koss et al reported that the stage of the disease did not affect survival, however the tumour size was strongly related to survival. Patients with tumours less and greater than 6 cm have 40% and 10% 5-year survival rates, respectively in their study [3]. Rahuoma et al reviewed a very large national database of almost 1,000,000 patients to compare pulmonary sarcomatoid carcinomas with non-small cell lung carcinomas with respect to clinicopathological features and surgical outcomes. They reported that 4987 patients with histological diagnosis of pulmonary sarcomatoid carcinomas presented with stages that are more advanced and worse survival outcomes. They concluded that surgery provided a survival advantage for pulmonary sarcomatoid carcinomas. However, they also stated that these tumors had a higher risk of recurrence and should be evaluated for novel adjuvant therapies [8]. The sarcomatous component of pulmonary carcinosarcomas is more progressively metastatic. Thus, a chemotherapy regimen targeting the sarcomatous component should be selected. On the other hand, sarcomatoid carcinomas showed a high rate of resistance to conventional first-line chemotherapy in a series of almost 100 patients [9]. Thus, the authors proposed new therapeutic strategies based on better knowledge of the carcinogenesis of sarcomatoid carcinomas. Radiotherapy is also a well-established choice of treatment, which can reduce the local recurrence rate in cases with residual tumor [10]. Our patient is free of disease during this six-month follow-up without any adjuvant treatment.

In summary, pulmonary carcinosarcoma is a very rare lung tumor histologically classified among the sarcomatoid carcinomas. Although a definitive treatment is unclear, surgery appears to have the most favorable outcome. Adjuvant treatments might be considered for a highly possible local recurrence and distant metastasis.

Declaration of conflicting interests

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Case Report

Poland's anomaly with contralateral spontaneous pneumothorax: is this a coincidence?

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ABSTRACT

Poland's syndrome is a rare developmental anomaly characterized by absence of pectoralis major muscle and presence of ipsilateral hand abnormalities (mostly syndactyly). Numerous malformations as a component of this syndrome was defined in literature such as congenital heart diseases, upper limb anomalies and pulmonary or renal hypoplasia. The incidence of Poland's syndrome ranges from 1 in 7,000 to 1 in 100,000 live births. Here we describe a rare case of patient with Poland's syndrome with contralateral spontaneous pneumothorax.

Key Words: Poland's anomaly, pneumothorax, congenital malformation

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Introduction

Although various abnormalities were defined as a component of Poland's syndrome in the literature, the characteristic features of this syndrome are absence of pectoralis major muscle and presence of ipsilateral hand abnormalities. Poland's anomaly with ipsilateral pneumothorax has been reported before as a very rare coexistence, but contralateral occurrence of pneumothorax is an extraordinary clinical situation and this case would be an important example of bilateral effect of Poland's syndrome on the lung parenchyma.

Case Report

58-years-old male admitted our emergency department with left chest pain, cough and shortness of breath. He was afebrile with a heart rate of 115/min, blood pressure of 125/75 mmHg, respiratory rate of 25/min and oxygen saturation of 80% on room air. His medical and family history was unremarkable. His social history revealed 10 pack-year cigarette smoking. The physical examination revealed a middle aged, dyspneic male, with an asymmetric chest wall due to hypoplasia of his right pectoral muscle and syndactyly in his right hand. His breathing sounds on auscultation were decreased over the left lung field. These clinical findings and chest radiogram (Figure 1) revealed Poland's anomaly with left sided pneumothorax. After the patient's clinical condition stabilized, hand radiography and thorax computed tomography were obtained (Figure 2).

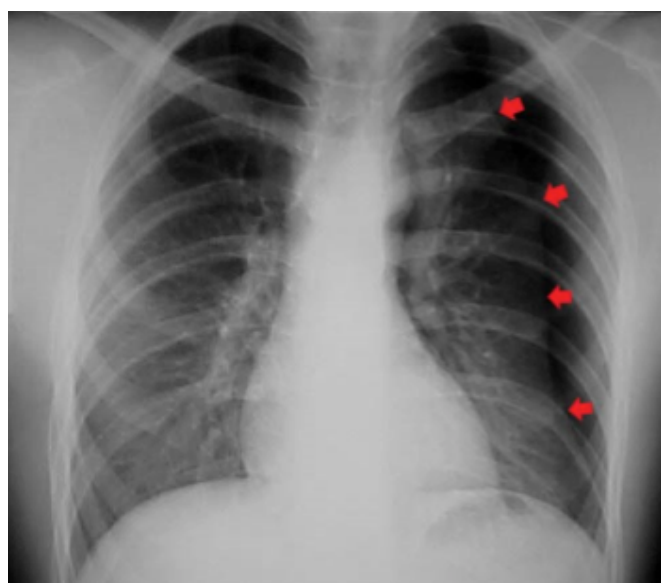


Figure 1. Chest radiogram reveal left pneumothorax (arrows).



Figure 2. Left pneumothorax and parenchyma line clearly seen in thorax CT image in the axial plane.

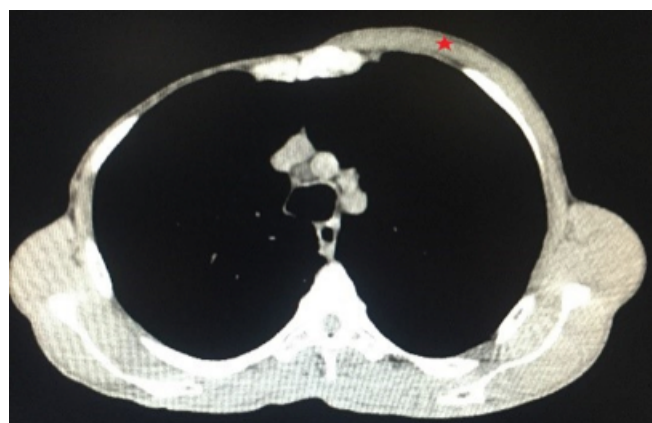


Figure 3. Thorax CT shows hypoplastic right hemithorax and absence of right pectoral muscle. Normal left pectoral muscle is seen in this image (asterix).



Figure 4. One of the clinical component of Poland's syndrome: hand abnormalities (absence of medial phalanges in right hand) Normal left medial phalanges are seen in this image (asterix).

Tube thoracostomy was performed from the fifth intercostal space on midaxillary line (Figure 5). His symptoms relieved after the intrapleural air was evacuated.

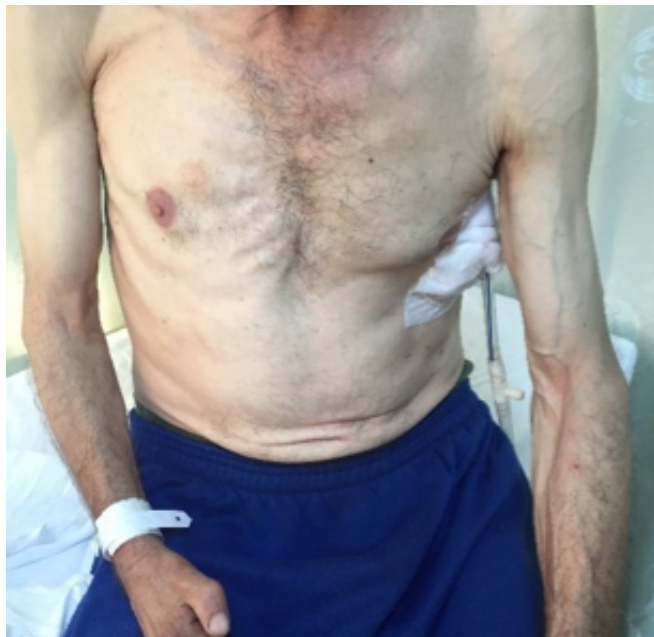


Figure 5. Unilateral chest wall hypoplasia and ipsilateral hand abnormalities.

Lung expansion was obtained on 4th day of drainage. Chest tube was removed and patient was discharged at 5th day of hospitalization.

Discussion

Alfred Poland described Poland's syndrome in 1841. Although chest wall hypoplasia and hand abnormalities were defined as the characteristic features of this syndrome, many other musculoskeletal anomalies would be seen like agenesis of the ribs and sternum, scoliosis, brachysyndactyly, mammary aplasia, and absence of the latissimus dorsi and serratus anterior muscles [1-3].

In literature, there are few reports about the familial occurrence of Poland's syndrome but, it was thought to be an intrauterine pathology rather than a genetic defect [4]. The etiology is unknown but hypoxia during in the sixth to seventh week of gestation is thought to be a main etiological factor causing hypoplastic or aplastic musculoskeletal abnormalities. The possible cause of the hypoxia would be arterial spasm or an arterial malformation [4,5].

Poland's anomaly with spontaneous pneumothorax has been previously reported only in few cases [6,7]. We detected only one case Poland's anomaly with contralateral spontaneous pneumothorax.

In literature, emphysema has been shown to be associated with spontaneous pneumothorax and it is defined as an "abnormal permanent enlargement of air spaces

distal to the terminal bronchioles". Main pathology is the destruction of lung's epithelial barrier causing a decrease in pulmonary elastic recoil. Cigarette smoke exposure is generally the main activator of destruction cascade. In addition, hypoxia would aggravate oxidative stress and protease production resulting emphysematous changes in the lung.

Considering the pathophysiology of Poland's syndrome based on hypoxia, etiological factors that cause this syndrome may also be responsible for the occurrence of bulla formation and emphysematous changes in lung. In addition, different brachial arch blood supply defects might be responsible for the contralateral occurrence of pneumothorax [7].

Consequently a little is known about the relationship between pathogenesis of Poland's syndrome and pneumothorax. More such should be presented to identify the relationship of these two diseases.

Declaration of conflicting interests

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Case Report

A rare case: extramedullary plasmacytoma of the mediastinum

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ABSTRACT

Plasmacytomas are localized proliferations of plasma cells in bone marrow. Extraosseous tissue involvement is uncommon. Herein, we report a case of mediastinal extramedullary plasmacytoma in a 54-year-old woman. A 85 mm lesion was reported in computed chest tomography of the patient who referred to our hospital with dyspnea. Since interventional radiologists did not think the patient was suitable for percutaneous biopsy, a surgical biopsy was performed and the pathology reported a plasmacytoma. Various investigations were done to rule out multiple myeloma. Since no result in favor of multiple myeloma was obtained, mass was diagnosed as extramedullary plasmacytoma. Radiotherapy was scheduled for the patient.

Key Words: extramedullary plasmacytoma, mediastinum, mediastinal mass

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Introduction

Malignant plasma cell dyscrasias occur due to the proliferation and differentiation of type B lymphocytes into autonomous, immunoglobulin producing plasmacytoid cells. Bence-Jones and Dalrymple first described it, in a patient with diffuse bone pain and proteinuria in 1846. Extramedullary plasmacytoma (EMP) is a plasma cell neoplasm of the soft tissue without having bone marrow involvement or other systemic features of multiple myeloma. EMP is a rare tumor and mostly detected in the upper aero-digestive tract. It is also very unusual for EMP to occur in mediastinum as a primary solitary lesion [1-5]. Herein we report an extremely unusual presentation of an EMP arising from the posterior mediastinum.

Case Report

A 54-year-old woman referred to our clinic with progressive dyspnea. Her surgical history includes appendectomy, cesarean section and a lumbar hernia operation. Her physical examination was considered normal except a lack of ventilation in the right hemithorax. No goiter, hepatosplenomegaly or significant lymphadenopathy was noticed. Laboratory blood tests revealed haemoglobin level 11.9 gr/dL, leukocyte level $3.2 \times 10^3/\mu\text{L}$ (neutrophils 53%, lymphocytes 35%, eosinophils and basophils both 0%) and thrombocyte level $136 \times 10^3/\mu\text{L}$. Her renal and liver functions were reported normal. The plain chest X-ray revealed a smooth, mass-like lesion in the right paratracheal region (Figure 1).



Figure 1. Preoperative chest x-ray of the patient.

Chest computerized tomography (CT) revealed a mass, which was spreading to the subcarinal and right paroesophageal regions. The size of the mass was 49×48 and 84×58 mm in the right paratracheal and retrocardiac areas, respectively (Figure 2).

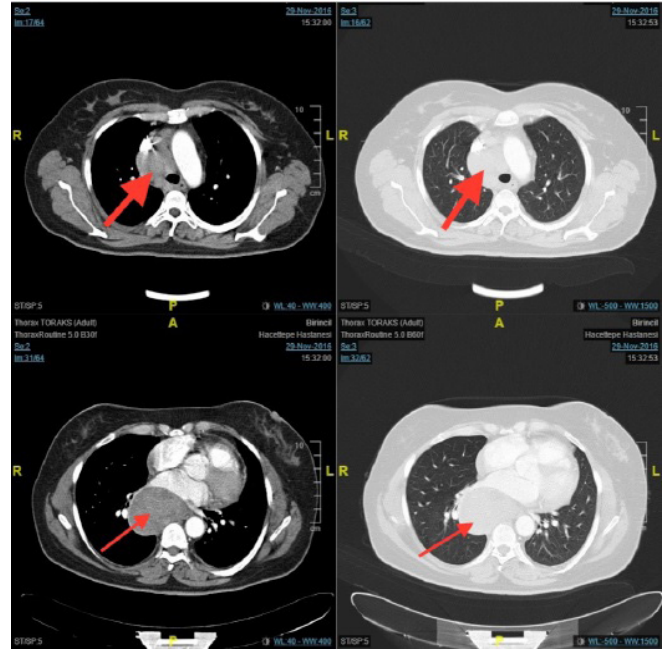


Figure 2. Thorax CT scan images showing the retrocardiac and the paratracheal locations of the mass in posterior mediastinum. The broad arrows in the upper images show the paratracheal location of the mass, as the thin arrows in the lower images point the retrocardiac location.

Positron Emission Tomography (PET) is performed and the SUVMax of the mass is found to be 2.9. No pathologic FDG involvement is reported for any other tissue. As transthoracic needle sampling was not recommended by the interventional radiology department, surgical biopsy of the mass was planned. Instead of minimally invasive methods such as EBUS or EUS, surgical procedures were considered convenient also due to the demand of the oncologist for a larger piece of specimen for further investigations. Since, single lung ventilation was not considered to be convenient by the anesthesiologists due to mass' pressure on trachea, thoracoscopic surgery options were called off and a 10 cm long, right limited thoracotomy was performed. A 10 cm mass was observed in the posterior mediastinum between the carina and esophagus. Due to the localization of the mass, its relation with the surrounding structures and the bleeding during the operation, complete resection

couldn't be performed. Multiple biopsies were taken for pathological investigation and the thoracotomy incision was closed routinely. The pathologic examination of the mass was reported as plasmacytoma with lambda light chain restriction. CD138, MUM-1 and lambda light chain immunohistochemical studies were reported positive while, CD3, CD68, CD34, CD20, kappa light chain and mast cell triptase were negative. The patient was consulted to the oncology department. During the evaluation in the oncology department her bone survey was studied. Neither focal lytic bone lesions, which might have been related to multiple myeloma, nor any vertebral collapse was noticed. Bone marrow biopsy was performed and revealed no pathologic pattern of cell distribution. Both serum and urine protein electrophoresis were performed and gamma peaks sighted. No M-protein or urine Bence-Jones protein was detected. Consequently, the tumor was diagnosed as a plasmacytoma and radiotherapy was scheduled.

Discussion

Extramedullary plasmacytomas (EMP) constitute approximately 3% of the plasma cell neoplasms. It is mostly seen around the 6th decade of life and 3-4 times more in men with respect to women [4]. EMP diagnosis is verified only if there is no evidence of multiple myeloma. To rule out multiple myeloma, there should be no histopathological evidence of plasma cell dyscrasia in bone marrow, with no clinical symptom such as bone pain, renal failure or anemia and in addition no presence of focal lytic bone lesions, which were all confirmed by CT, bone survey, bone marrow aspiration investigation and blood tests in our case [2,6]. Plasma cell neoplasms are considered more sensitive to radiotherapy with respect to other types of treatment. Mostly surgical resection of the tumor is combined with RT. Most of the patients are cured after surgery and RT. Local recurrence is shown in nearly 30% of the patients. In 40% of the patients, multiple myeloma emerges. An increase in

the baseline level of serum monoclonal proteins or detection of Bence-Jones protein in urine may signify the recurrence of the disease or the onset of multiple myeloma. Dissemination into multiple myeloma has been reported in 10-30% of the patients with EMP in the first 2 years [3,7]. Thus, long-term follow-up is mandatory in these rare tumors.

Declaration of conflicting interests

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Case Report

A rare cause of mediastinal mass: tuberculosis

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ABSTRACT

Neoplastic and non-neoplastic pathologies can cause lesions in the mediastinum. Bronchogenic cysts, germ cell tumors, lymphoma, lymph node hyperplasia, thymoma, thymic cysts, and thyroid masses tend to develop in mediastinal compartments. Tuberculosis would cause lymph node enlargement in many areas of the body but it is a very rare cause of mediastinal mass. We report a case of tuberculosis presenting with isolated, large middle mediastinal mass with high FDG uptake in PET/CT. We also present a short review of reported cases of mediastinal tuberculosis.

Key Words: mediastinal mass, tuberculosis, video-assisted thoracoscopic surgery

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Introduction

The mediastinum is the central compartment of the thoracic cavity that was divided into three compartments as anterior, middle and posterior. Different anatomical classifications of the mediastinum are reported in the literature [1]. These classifications are helpful in clinical practice to classify the mediastinal pathologies.

The middle mediastinum is located in between pericardium in anterior and vertebral body in posterior. Bronchogenic cysts, bronchogenic tumors, lymph nodes, vascular masses and pleuropericardial cysts tend to develop in this mediastinal compartment. Tuberculosis would cause lymph node enlargement in different parts of the body, but it is very rare cause of mass in the middle mediastinum [2]. We report a case of tuberculosis that presenting with isolated, large middle mediastinal mass with high FDG uptake in PET/CT.

Case Report

A 67-year-old female presented with complaints of breathlessness and chest pain for the last four months was referred to our department. The patient was a non-smoker, and there was not any history of chronic illness, prior hospitalization or surgery. Her family history was also non-significant. The laboratory tests showed only leukocytosis ($13.0 \times 10^9/L$) and mild anemia (hemoglobin 11g/dL). Chest radiogram revealed mediastinal enlargement, so thorax computed tomography is taken. Thorax CT is revealed a 6x7 cm solid, homogeneous, smoothly limited mass located in the paratracheal region in the middle mediastinum (Figure 1).



Figure 1. 6x7 cm solid, homogeneous, smoothly limited mass located in right paratracheal region.

There were no invasion of structures such as the phrenic nerve, major vascular structures, lung, or sternum. To differentiate malign and benign conditions, PET-CT reported a high FDG uptake (Figure 2).

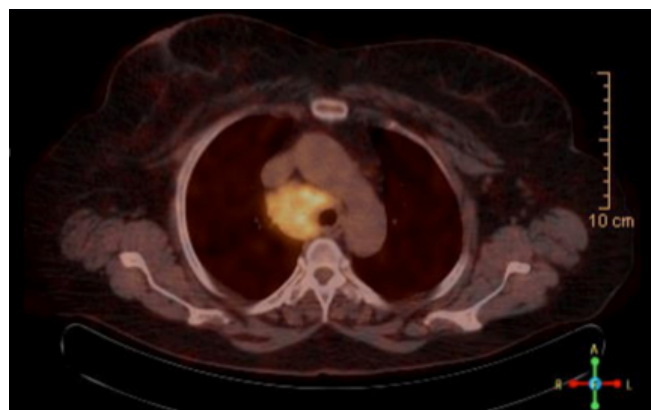


Figure 2. PET-CT demonstrate high FDG uptake in the mass.

Because of the paratracheal localization of the mass, EBUS-TBNA is performed, but the diagnostic sample could not be obtained. So surgical excision was planned to make a definite diagnosis and alleviate symptoms of the mass effect.

Surgical Technique

Video-assisted thoracoscopic surgery was performed with a selective intubation. The first incision, about 3-4 cm long was performed at the 4th intercostal space in the mid-axillary line to have a good access for the dissection of the middle mediastinum. The second incision was performed in the 7th intercostal space, in the mid-axillary line and was used as a camera port. The thoracic cavity was inspected visually and mediastinal, paratracheal mass was seen as surrounded by the mediastinal pleura above the level of the azygos vein (Figure 3).

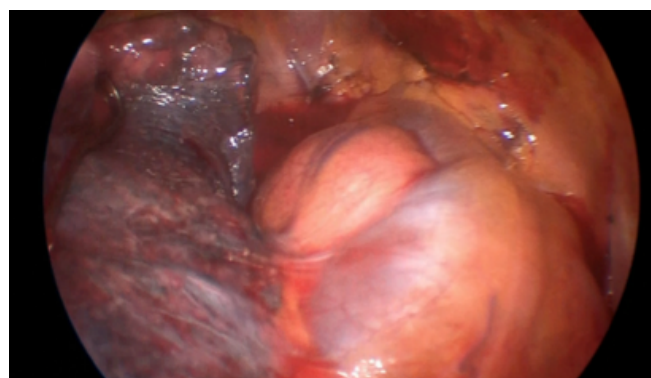


Figure 3. Mediastinal, paratracheal mass is seen as surrounded with mediastinal pleura above the level of the azygos vein.

Mediastinal pleura was incised and the mass was freed up from superior vena cava and azygos vein with blunt and sharp dissection. The mediastinal mass was totally excised and the rapid diagnostic procedure performed via frozen section (Figure 4).

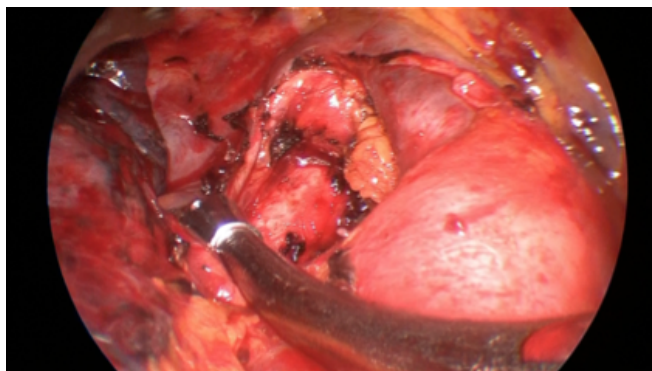


Figure 4. Paratracheal region; seen after total excision of the mediastinal mass.

The frozen section reported that, the mass excised from middle mediastinum is a granulomatous lymph node secondary to tuberculosis infection (Figure 5).

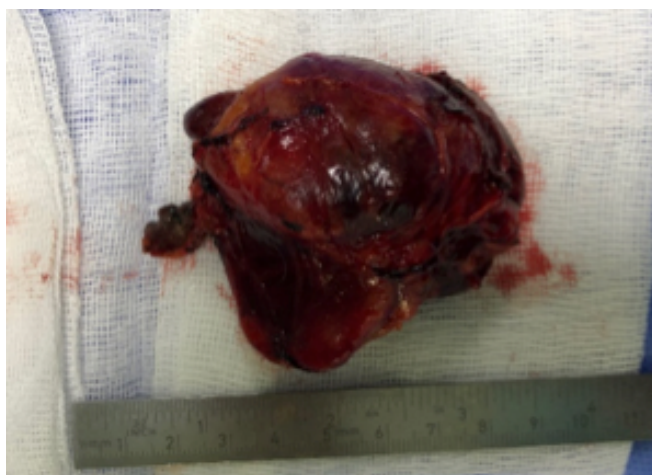


Figure 5. A 6x7 cm solid mass was reported as granulomatous lymph node by frozen section.

After the air leakage and hemorrhage control, a 28 French chest tube was inserted into the thoracic cavity through the camera port.

Postoperative Follow-up

The postoperative course was uneventful. The chest tube was removed on the post-operative day 2, and the patient was discharged on the postoperative third day.

Discussion

Neoplastic and non-neoplastic pathologies can cause lesions in the mediastinum. It is usually difficult to make a definitive diagnose due to the wide range of etiologies. Bronchogenic cysts, bronchogenic tumors, lymph nodes, vascular masses and pleuro-pericardial cysts may present as a large mass in the middle mediastinum

[1]. In most of the cases patients don't have any symptoms and mediastinal lesions are usually detected incidentally. If the lesion is large enough to make a compression to neighboring structures clinical presentations like chest pain, dyspnea and cough would be seen.

Chest computed tomography (CT) is a valuable imaging modality for the evaluation of mediastinal masses. Also, magnetic resonance imaging (MRI) are used to distinguishing cystic from solid masses and to prove invasion to mediastinal structures especially in malign conditions.

Fluorodeoxyglucose (FDG) - positron emission tomography (PET) is helpful to make a differential diagnosis and evaluation of treatment response, especially in malign conditions like thymoma and germ cell tumors. Because of metabolic activity of inflammatory cells are increased FDG uptake also seen in a granulomatous disease like sarcoidosis and tuberculosis. Tuberculosis is the common cause of peripheral lymphadenopathy, especially in developing countries. However, tuberculosis presenting as a large mediastinal mass is a rare condition.

In literature 11 cases of isolated mediastinal mass were reported [3-13]. In four cases, mediastinal mass was excised with thoracotomy. In other cases only a punch biopsy was performed (Table 1).

Table 1. Review of the literature, 11 case reports in which isolated mediastinal mass was diagnosed as tuberculosis.

		Age	Diagnostic procedure
Vincken et al.	1983	40 years	Thoracotomy (total excision)
Thirithuvathas et al.	1989	2 years	Thoracotomy (total excision)
Ahmed et al.	2001	10 month	Thoracotomy (total excision)
De Ugarte et al.	2003	3 month	Thoracotomy (total excision)
Maeder et al.	2003	22 years	Mediastinoscopy (biopsy)
Gillies et al.	2008	7 month	Thoracoscopy (biopsy)
Boussetta et al.	2010	3 month	Thoracoscopy (biopsy)
Khilnani et al.	2011	14 years	FNA (biopsy)
Kumar et al.	2013	76 years	FNA (biopsy)
Jain N et al.	2013	33 years	FNA (biopsy)
Maguire et al.	2016	22 years	Mediastinoscopy (biopsy)
Batihani et al.	2018	67 years	Video-assisted thoracoscopic surgery (total excision)

To the best of our knowledge, this might be the first case of total excision of a mediastinal mass with VATS

procedure and diagnosed as tuberculosis,. The important point for performing a VATS procedure is the advantage of decreased postoperative pain and a shorter hospital stay as known [14].

Total excision of a mediastinal tuberculosis is not necessary in all cases. However, if the patient has compression signs and the diagnostic sample could not be obtained with biopsy, surgical excision should be needed.

In conclusion, establishing the etiology of mediastinal masses can be difficult. Imaging techniques including CT, MRI, and PET-CT narrow the possible causes, but definitive diagnosis is performed only with histopathological verification. If total excision is planned, VATS is a safe and feasible procedure even for large masses as in our case. We aimed to present this case in the immunocompetent patient presenting with an isolated mediastinal mass. We also recommend the use of VATS when surgical excision is required.

Declaration of conflicting interests

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ures with capitalization and unabbreviated (e.g., “As shown in Figure 2...”, and not “Fig. 2” or “figure 2”). The tables and figures themselves should be given at the end of the text only, after the references, not in the running text.

The resolution of images should not be less than 118 pixels/cm when width is set to 16 cm. Images must be scanned at 1200 dpi resolution and submitted in jpeg or tiff format. Graphs and diagrams must be drawn with a line weight between 0.5 and 1 point.

Graphs and diagrams with a line weight of less than 0.5 point or more than 1 point are not accepted. Scanned or photocopied graphs and diagrams are not accepted.

Charts must be prepared in 2 dimensions unless required by the data used. Charts unnecessarily prepared in 3 dimensions are not accepted.

Figures that are charts, diagrams, or drawings must be submitted in a modifiable format, i.e. our graphics personnel should be able to modify them. Therefore, if the program with which the figure is drawn has a “save as” option, it must be saved as *.ai or *.pdf. If the “save as” option does not include these extensions, the figure must be copied and pasted into a blank Microsoft Word document as an editable object. It must not be pasted as an image file (tiff, jpeg, or eps) unless it is a photograph.

Tables and figures, including caption, title, column heads, and footnotes, must not exceed 16×20 cm and should be no smaller than 8 cm in width. For all tables, please use Word’s “Create Table” feature, with no tabbed text or tables created with spaces and drawn lines. Please do not duplicate information that is already presented in the figures.

Tables must be clearly typed, each on a separate sheet, and double-spaced. Tables may be continued on another sheet if necessary, but the dimensions stated above still apply.

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