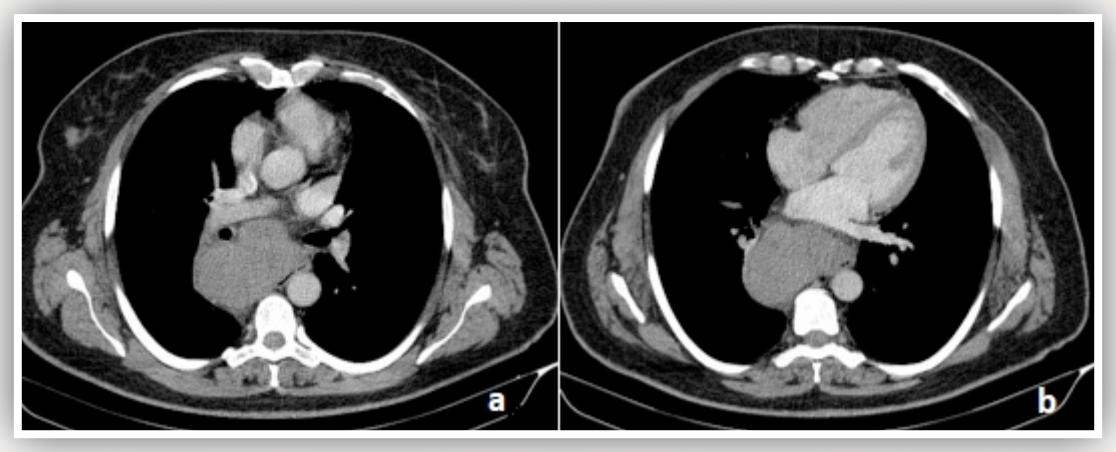
Volume 5 Number 1 April 2020 eISSN 2548-0316

CURRENT THORACIC SURGERY



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Curr Thorac Surg

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Official e-Publication of:

Turkish Society of Thoracic Surgery (TSTS)

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Volume 5 Number 1 April 2020 e-ISSN 2548-0316

To cite this article: Sungur Z. Anesthetic management of patients with COVID-19. Curr Thorac Surg 2020; 5(1): E1-E4.

Editorial

Anesthetic management of patients with COVID-19

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Nowadays, we have to face an unexampled outbreak associated with more than 1 million over the world and with quite high mortality. Health systems are solely focused on this pandemic, which is globally out of control. Although the majority recovers with mild to moderate symptoms, pneumonia may ensue with respiratory failure. Healthcare providers and especially anesthesiologists constitute the frontline of this outbreak. It is actually very dynamic period with more questions than responses despite several publications worldwide. Meanwhile ultra-high spread and transmission ways are mostly determined. This article is a modest introduction about COVID-19, focusing mainly on precautions, which should be adopted by medical staff most vulnerable to this infection.

A novel pneumonia was initially described in December 2019 at Wuhan, and China reported World Health Organization (WHO) country office about unknown pneumonia. It would be later attributed to a novel coronavirus. The disease was subsequently named as "coronavirus disease 2019" or as commonly called COVID-19. On the last days of January, the first cases of COVID-19 were enrolled in Italy, and a terrifying cluster ensued in Lombardy. Outbreak gained a global aspect with new cases in Europe and in Asia.

At first days of February, China reported more than 20.000 patients. Owing to the rapid spread of the disease, WHO proclaimed pandemic on 10 March with a situation report. Organization Director highlighted the importance of readiness, detecting modalities, protection and reducing transmission in his global message. Furthermore, COVID-19 reached America with the United States, Canada, Brazil, Chile as well as Australia and New Zealand. The first case was declared on 11 March in Turkey. Actually more than 200 countries are involved about 1.2 million patients and more than 60.000 deaths (in the first days of April).

The pathogen belongs to the Betacoronavirus family existing about 5000 years on earth and known to be associated with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) [1]. The name is related to the crown-like view of S proteins under electron microscopy. It is an enveloped RNA virus, which seems to use angiotensin converting enzyme 2 receptor via S protein similar to SARS. These receptors are situated particularly in the lung but also in intestines, myocardium or vessels.

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Doi: 10.26663/cts.2020.00011
Received 05.04.2020 accepted 06.04.2020
Provenance and peer review: This article was commissioned by the Editorial Office, Current Thoracic Surgery. The article did not undergo external peer review.

Animal species might be considered as a host of coronavirus. However, human-to-human transmission is achieved mainly by respiratory droplets. Oral- fecal transmission is conceivable as the virus can replicate in the gastrointestinal system [2]. Symptomatology of coronavirus family can be explained by the structural differences of their proteins, tropism or replication procedures. When it enters the target cell, RNA replication succeeds while shielding from host defense.

The reproductive number (R0) which means the expected numbers of patients by an initial infected person, is 2-2.5 [3,4]. Initial data reported that infected individuals double every 7.4 days [5]. The incubation period is generally 4 to 7 days (2-14 more exactly). It can be affected by host characteristics, or by the phase of the epidemic [6].

Reverse transcriptase polymerase chain reaction is the standard testing method. Throat or nasal swabs are used for diagnosis with an initial positive rate of 30-60%. This limitation could be ameliorated with serial sampling.

The clinical course of COVID-19 represents a large spectrum from mild to severe either fulminant form. Fever and dry cough are the commonest symptoms of about 85-90% [6,7]. Other non-specific signs are myalgia, fatigue, headache, diarrhea, etc. Asymptomatic infected individuals have a key role in transmission.

Subjects with mild clinical course have generally good prognosis. About 15 to 20% of infected patients would have pneumonia. Shortness of breath can warn about a serious outcome. Radiographic findings are well established with the bilateral and peripheral location as ground glass opacities. Radiologic patterns may become "crazy- paving" with the progression of the disease. Leukopenia and especially lymphopenia are frequent. Lower antithrombin, and higher D-dimer values are other hematologic changes and associated with severe disease [8].

Clinical features and therapy of pneumonia is a hot topic, which needs to be updated too often and should be largely interpreted in another article.

The main transmission mechanism is via droplets or airborne, healthcare providers working in a milieu open to patients' respiratory secretions are at increased risk of infection. The next part of this article would focus on high-risk procedures and personal precautions necessary for staff.

High-risk procedures to generate aerosol are mainly defined as tracheal intubation or surgical airway, bag mask ventilation, non- invasive ventilation procedures (CPAP, high flow) and bronchoscopy [9]. Cardiopulmonary resuscitation, circuit disconnection, and tracheal extubation are similarly associated with a high risk of aerosol generation. General precautions are aimed to define explicitly airway strategies, to prepare and to utilize guidelines, to isolate high risk areas for aerosol generating medical procedures (AGMP) -create hot, warm and cold zones- and to limit staff during these procedures. It is also crucial to educate all staff -not only medical ones- for transmission ways, institutional logistic decisions and safety measures. At last but not least, surgery is feasible only if it becomes lifesaving.

Operating room (OR) dedicated to COVID-19 patients should rather have a negative pressure system with adequate pressure levels. Organization for OR includes the distinction of dirty, clean buffer or clean zones. The dirty zone is accessible for two anesthesiologists, surgeon, and assistant(s), nurse(s). They have to be armed with full protection including goggles (or face shielding), appropriate masks (N95/ FFP 2 and FFP 3), fluid resistant gown and double gloves [9-13]. Hand washing or the use of quick disinfectants are suitable for each step [11]. A 'buddy system' to ensure correct preparation in clean the buffer zone is recommended [10]. Assistants for anesthesia and surgical teams wait and help in the clean buffer zone, they are equipped with standard masks and scrubs. It is essential to remind that no staff should enter or exit until the case ending. It could be allowed unless adequate precautions are established. Anesthetic and surgical runners are located in the clean zone.

Spinal anesthesia in COVID-19 constitutes an alternative for limited procedures (Caesarean section or lower-limb surgery) [14]. Otherwise, endotracheal intubation is mandatory omitting facemask or supraglottic airways. During the endotracheal intubation period, limiting staff -with two anesthesiologists- is preferred to minimize viral exposure. Pre-oxygenation with 100% for 5 minutes is suitable for prolonged apnea period.

The patient's mouth and nose should be shielded by two layers of wet gauze or transparent covers to minimize droplet dispersion. Rapid sequence induction is largely recommended [10-14]. Rocuronium (1-1.2 mg.kg-1) is the first alternative for neuromuscular blocking, suxamethonium could be used with a dose of 1.5 mg.kg-1 considering apnea time and risk of coughing [10]. Video-laryngoscopy is vital to protect anesthesiologist with a safer distance of infected patient's airway. An experienced anesthesiologist assumes for smooth intubation and the second one should immediately inflate tube balloon. A clamp to the endotracheal tube (ETT) or exhalation filter should be prepared before intubation. Confirmation of ETT has easily achieved with end-tidal CO2 tracing. An epidural filter can be used in streamline end-tidal CO2 sampling lines. Leakage should be monitored and avoided. All airway equipment should be available in dirty or clean buffer zones according to difficult airway predictions. If difficult airway is suspected, anesthesiologists should consider guideline recommendations, their resources and patient's status. Awake intubation is possible within experienced teams but potentially associated with increased aerosol generation. Insertion of the supraglottic airway with subsequent ETT placement can be another alternative [10].

It would be clever to use COVID-19 dedicated anesthesia machines with high efficiency filters on both inspiratory and expiratory limbs. Two HME filters could be placed next to ETT. If surgery lasts more than 4 hours, filters should be changed. Anesthesia machine, monitors, pumps should all covered by packs with the availability of control panel. Carbon dioxide absorbent should be replaced at the end of cases.

Tracheal extubation is an AGMP as well. Coverage or wet gauze layers should be placed. Recovery should be as smooth as possible to prevent coughing and secretions. One of the filters is removed with ETT, and the second is immediately joined to face mask. When adequate spontaneous ventilation is established, the patient can be transferred from OR to ward with a face mask and O2 supply if necessary. If the postoperative course requires a planned ICU stay, then a team with personal precautions would transport following dirty zone instructions. Removal of protective equipment begins in the clean buffer zone from goggles to gown, protective mask and head cover with handwashing in each step.

In conclusion, this global outbreak represents a big problem for health care systems. Medical staff should aware of the mode of transmission, protective measures and thereby execute appropriate changes in hospitals. Appropriate preparation, meticulous control, strict submission to precautions are essential for the health and safety of frontline workers as anesthesiologists.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethical Statement

The author are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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To cite this article: Çınar HU, Kocatürk C, Cansever L, Ceyhan S, Bedirhan MA. Morbidity, mortality and survival rates of non-small cell lung cancer patients who underwent lobectomy with pulmonary artery reconstruction compared to those of the patients who underwent pneumonectomy. Curr Thorac Surg 2020; 5(1): 1-9.

Original Article

Morbidity, mortality and survival rates of non-small cell lung cancer patients who underwent lobectomy with pulmonary artery reconstruction compared to those of the patients who underwent pneumonectomy

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ABSTRACT

Background: Pulmonary artery reconstruction can be preferred as an alternative to pneumonectomy, to spare the functional lung parenchyma in lung cancer. This study aimed to evaluate the morbidity, mortality and survival rates of the patients who had undergone pulmonary artery reconstruction due to central non-small cell lung cancer (NSCLC) and also to compare their data with those of the patients who had undergone pneumonectomy.

Materials and Methods: In this study, 88 patients who underwent pneumonectomy (group PN) and 20 patients who underwent standard or sleeve lobectomy (double sleeve) with pulmonary artery reconstruction (group PAR) for NSCLC with stages I-IIIA between January 2005 and December 2010 were evaluated retrospectively. The morbidity and mortality rates, durations of the hospital and intensive care unit stay, 5-year and mean survival rates of the homogenous patient groups were analyzed comparatively.

Results: The postoperative morbidity rate was 30% in the PAR group and 53% in the PN group ($p = 0.77$). The bronchial complication rate was 0% in the PAR group and 15% in the PN group ($p = 0.04$). The 30-day mortality rate was 5% in the PAR group and 5.6% in the PN group ($p = 1$). The median follow-up period for all patients was 31.5 months (range: 0-84 months) and total 5-year survival was 56.2%. In early-stage tumors (stage I + stage II), total 5-year survival rate was 64% in the PAR group and 60% in the PN group ($p = 0.7$). In late-stage tumors (stage III), total 5-year survival rate was 52% in the PAR group and 30% in the PN group ($p = 0.04$). No local recurrence was observed in either group during the follow-up period.

Conclusions: In central lung tumors, to avoid pneumonectomy, major anatomical lung resection with pulmonary artery reconstructions can safely be performed with acceptable morbidity and mortality rates. Oncological outcomes of pulmonary angioplasty procedures regarding survival and local recurrence are not worse than those of pneumonectomy. Even in advanced stage lung tumors, these procedures can be an alternative to more radical operations such as pneumonectomy.

Keywords: pulmonary artery resection, pulmonary angioplasty, lung cancer, bronchoplasty, pneumonectomy

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Doi: 10.26663/cts.2020.0001
Received 18.06.2019 accepted 07.08.2019

Introduction

Pneumonectomy has been performed as a standard surgical method in the curative treatment of patients with central lung tumors for decades, [1]. The limited physiological reserve after pneumonectomy (PN) is considered to cause higher morbidity and mortality than lobectomy [2-6]. Since the sparing of functional lung parenchyma provides a higher quality of life, bronchial sleeve resections have been used as an alternative to pneumonectomy in central lung tumors [7,8]. In many comparative publications up to date, the perioperative risk of bronchial sleeve resection is shown to be comparable to that of standard lobectomy [9-11], and it has been noted that its long-term survival outcomes and tumor recurrences are similar to or better than pneumonectomy [10,12,13]. Knowing that pneumonectomy alone is a mortality-increasing operation, it has recently been reported that independent of pulmonary functions, parenchyma sparing surgeries (PSS) are also widely performed in patients who can tolerate pneumonectomy [1,14].

The only alternative to pneumonectomy is pulmonary artery reconstruction (PAR) combined with lobectomy or bronchoplasty if there is main pulmonary artery involvement in the central pulmonary tumors, [15]. Although high mortality and morbidity rates have been reported in the early reports of this parenchyma sparing lung resection [16], the advantages of pulmonary angioplastic procedures have been shown in recent studies [17-20], and thus these applications have become increasingly popular in lung cancer surgery. Especially, the increase in the long-term satisfactory results of the bronchovascular sleeve resections [1,15,17,18,20-23] has been the basis of pulmonary angioplasties performed to avoid pneumonectomy in central lung tumor patients with pulmonary artery invasion. However, in the literature, there are only a few clinical studies comparing pneumonectomy performed with angioplasty procedures in terms of operative mortality, morbidity, survival and recurrence rates [1,21,24-27]. In these studies, PAR has generally been applied to heterogeneous patient populations with different surgical techniques for different indications, and it has been considered as a variation of bronchoplastic procedures (extended sleeve) when comparing its results with the results of the patients who underwent PN; therefore, it is difficult to make a precise interpretation about the superiority of PAR itself to PN.

This retrospective study aims to investigate the patients who underwent pulmonary artery reconstruction due to central non-small cell lung cancer (NSCLC) with pulmonary artery involvement in terms of morbidity, mortality and survival rates and to compare these results with the results of the patients who underwent pneumonectomy in the same period.

Materials and Methods

All of the patients who were treated in our clinic gave informed consent by signing a statement allowing the use of their data for clinical trials. The study was approved by the institutional review board (2019-004-002) and was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Criteria

In the study; six hundred and thirty-six patients who were diagnosed with NSCLC, ranging from stage I to III A, and underwent lung resection in Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital between January 2005 and December 2010 were analyzed. Among these, a total of 139 patients were studied retrospectively, of whom 22 had undergone pulmonary artery reconstruction, and 117 had undergone pneumonectomy. Data collection for analysis was ended in November 2012.

Tangential resection and primary suturation of the pulmonary artery (PA), patients with simple closure of a single PA branch or PA damage repair, patients who received neoadjuvant therapy, patients with 'T4' tumor, patients who had 'N2' lymph node metastasis or R1 microscopic residual disease, patients who underwent extended resection such as chest wall resection or carina resection, carcinoid tumors, lung tumors with the brain and surrenal metastasis, patients who were operated for recurrent lung tumors and completion pneumonectomy were excluded from the study for the sake of homogeneity between the groups. In conclusion, 20 patients (group PAR) who underwent pulmonary artery reconstruction and 88 patients (group PN) who underwent pneumonectomy in the same period were included in the study.

Preoperative Preparation

All patients underwent the standardized diagnostic and staging procedures preoperatively. Histopathological diagnostic specimens were obtained by either fiberoptic

bronchoscopy or computed tomography (CT)-guided needle biopsy. CT scans of each patient's chest and upper abdomen, bone scintigraphy, and brain magnetic resonance imaging (MRI) or Positron-emission tomography (PET) study were performed for noninvasive staging. Each patient also underwent a pulmonary function test, electrocardiography, and arterial blood gas analysis to evaluate the operative risk. Pulmonary angiography was performed in selected cases to evaluate the degree of pulmonary artery invasion. All patients suspected of having N2-N3 lymph node metastasis underwent cervical mediastinoscopy-mediastinotomy-extended mediastinoscopy.

Surgical Method

Single-lung ventilation was established through a double-lumen endotracheal tube. A routine posterolateral thoracotomy in the fifth intercostal space was performed. Mediastinal and hilar lymph node dissection was routinely performed, and frozen sections were studied. Patients who had a central tumor in the entrance of lobar bronchus and who had positive surgical margin after standard lobectomy underwent bronchoplastic procedure in which end-to-end style anastomosis was performed using a continuous suturing technique with 3-0 non-absorbable material (Prolene Ethicon Inc, Hamburg, Germany). Where safe dissection of pulmonary artery branches was not possible due to tumor invasion, but complete surgical resection with standard or sleeve lobectomy could be achieved, patients underwent PA resection and reconstruction procedures to avoid pneumonectomy. After the resection of the tumor-effected part of the PA, bronchus was also resected, and the tumor-bearing lobe was removed en-block. Meanwhile, frozen section examinations were performed both for the bronchus and for the resected part of the PA to be sure that there was no tumor at the margins of the resection.

At the pulmonary artery reconstruction phase, patch angioplasty was performed if PA diameter was resected up to the half; if more than half of the PA diameter was resected, sleeve angioplasty (sleeve resection and end-to-end anastomosis) was performed. In all patients who underwent patch angioplasty, the autologous pericardium removed from the anterior part of the phrenic nerve was used for patching. The graft was patched using continuous suture technique with 5-0 monofilament non-absorbable material (Prolene Ethicon Inc, Hamburg, Germany). If a concomitant bronchoplastic procedure would also be performed, patch angioplasty was performed before the bronchial anastomosis to reduce the clamping time of the pulmonary artery. In sleeve angioplasty requiring patients, PA anastomosis was performed after the bronchial anastomosis to minimize vascular manipulation and to shorten the distance between the distal and proximal edges to decrease the tension. Pulmonary artery anastomosis was performed using a continuous suture technique with 5-0 monofilament non-absorbable material (Prolene Ethicon Inc, Hamburg, Germany). In double sleeve performed patients, pedicled pericardium or pleural flap was interposed between the tissues of the anastomosis. In the pneumonectomy group, closure of the main bronchus after resection was performed with two or four rows of 3-0 non-absorbable suture (Prolene Ethicon Inc, Hamburg, Germany). All patients included in the study were extubated on the operation room and were transferred to the intensive care unit.

Postoperative Period

Fiberoptic bronchoscopy was performed in the postoperative period if the patient developed secretion retention or if any anastomotic complications were suspected. In PAR group, long-term oral anticoagulation was not considered necessary in patients who underwent patch angioplasty. However, patients who underwent sleeve angioplasty received IV heparin during hospitalization and oral anticoagulant for 3 months following discharge to prevent clot formation due to anastomotic turbulence.

Postoperative histopathological staging (pTNM) was performed. The resected specimen was examined histopathologically and the histologic type was determined according to the WHO classification [28]. Surgical pathological staging was performed according to the 7th TNM grading system adopted by the American Joint Committee for Cancer (AJCC) in 2009 [29]. Routine postoperative follow-up included an office visit with a physical examination, serial chest radiographs, and computed tomography every 3-6 months.

Postoperative complications, days of postoperative stay in intensive care, and postoperative hospitalization were considered as morbidity indications [24]. The development of any fatal complications within the postoperative 30 days or death before discharge was defined as postoperative mortality. The day the patient underwent operation was taken base for the survival analysis, and

the calculation was made according to it. Any tumor or mediastinal lymph node development having the same histology as the original tumor in the resected hemithorax was defined as the local recurrence of the disease.

Statistical Analysis

Demographic data, morbidity and mortality rates were calculated as percentages and compared using the X2 or Fisher's Exact test. Kaplan-Meier survival analysis was used for survival and Mann Whitney U test for continuous variables. P-value of less than 0.05 was considered to be statistically significant. SPSS 10.0 packaged software was used for analysis.

Results

1. Characteristic Features

Similar general characteristics of patients are given in Table 1.

Table 1. Clinical and pathological features of the patients.

	PAR	PN	p
Total patients, n	20	88	
Age (years ± SD, range)	56.70 ± 7.4	57.15 ± 8.9	0.81
Gender (n ,%)			
Male	18 (90)	86 (97)	0.12
Female	2 (10)	2 (3)	
Mediastinoscopy (n, %)	18 (90)	78 (88)	1
Comorbidities (n ,%)	11 (55)	33 (37)	
Hypertension	3	14	0.47
COPD	3	6	
Diabetes Mellitus	2	6	
Atherosclerotic heart disease	2	4	
Side of operation (n, %)			
Right	3 (15)	34 (38)	0.04
Left *	17 (85)	54 (62)	
Histologic type (n, %)			
Squamous cell carcinoma	16 (80)	67 (76)	0.45
Adenocarcinoma	2 (10)	17 (19)	
Other	2 (10)	4 (5)	
pTNM staging (n, %)			
IA	0	0	0.83
IB	3 (15)	10 (11)	
IIA	8 (40)	30 (34)	
IIB	4 (20)	22 (25)	
IIIA	5 (25)	26 (29)	
Adjuvant therapy (n, %)			
Chemotherapy	10 (50)	29 (32)	0.25
Radiotherapy	2 (10)	4 (4.5)	
Combined therapy	1 (5)	10 (11)	

Abbrev.; COPD: chronic obstructive pulmonary disease, SD: standard deviation.
**Indicates a significant difference between two groups.*

Although both groups underwent left-dominant operations, this dominance was statistically significant in PAR group (p = 0.04). Types of concomitant resections and angioplasties performed on the patients in PAR group (n = 20) are given in Table 2.

Table 2. Types of concomitant resections and angioplasties performed in PAR group.

	Partial resection + patch plasty	Sleeve resection + end-to-end anastomosis	Total (n , %)
Standard lobectomy	9	_	9 (45)
Sleeve lobectomy	1	10	11 (55)
Total (n , %)	10 (50)	10 (50)	20 (100)

Together with pulmonary angioplasty, nine patients underwent standard lobectomy (left upper lobectomy, n=7; right upper lobectomy, n=1; right lower lobectomy, n=1), eleven underwent sleeve lobectomy (left sleeve upper lobectomy, n=10; right sleeve upper bilobectomy, n = 1). In all patients who underwent double sleeve lobectomy, a left-sided procedure was performed. All patients underwent PAR due to direct tumor invasion. Of the thirty-four right pneumonectomies, five were intrapericardial (14%); of the fifty-four left pneumonectomies, nine were intrapericardial (16%). Of the patients, fifty-six underwent pneumonectomy due to fissure invasion, 12 (left pneumonectomy, n = 8; right pneumonectomy, n = 4) due to vascular invasion, and 20 due to main bronchial tumor.

2. Morbidity Indications

Postoperative complications used as indications of morbidity were evaluated, and they were summarized in Table 3.

Table 3. Peroperative complications as indicators of morbidity.

	PAR (n=13)	PN (n=81)	p
Minor			
Arrhythmia	1	7	0.54
Secretion retention	4	23	0.32
Prolonged air leakage > 7 days	3	0	-
Major			
Pneumonia	2	12	0.61
ARDS	1	7	1
Broncho-pleural fistula	0	14	0.04*
Hemorrhage-Hematoma	1	6	0.73
Empyema	1	12	0.35

Abbrev.; ARDS: adult respiratory distress syndrome.
**Indicates a significant difference between two groups.*

In the PAR group, 13 complications (8 minor, 5 major) developed in six patients and the morbidity rate was 30%. In the PN group, 81 complications (30 minor, 51 major) were observed in forty-seven patients and the morbidity rate was 53%. When groups were compared, there was no significant difference in morbidity rates (p = 0.77), although, more patients in the PN group had more complications.

The most frequent complications in both groups were pulmonary complications. The most common cause of pulmonary complications in both groups (group PAR, n = 4; group PN, n = 23) was secretion retention/ atelectasis requiring FOB or nasotracheal aspiration (NTA). No significant difference was observed between the groups in terms of therapeutic FOB requirements (p = 0.32).

No bronchial dehiscence or late-term non-neoplastic stricture development was observed in PAR group patients, while in the PN group 14 (15%) patients developed a broncho-pleural fistula. Of the patients with fistula, 10 underwent right PN and 4 left PN. A significant difference observed between the groups in terms of bronchopleural fistula development (p = 0.04).

Pleural drainage and irrigation were performed on 14 patients who developed BPF in the PN group; via thoracostoma in seven and tube thoracostomy in 3. Two patients underwent stump revision and omentoplasty, and of the remaining 2; 1 underwent sternotomy with bronchial occlusion in the early period, and the other underwent endobronchial closure with FOB.

No significant difference was observed between the hospital stays of the patients in PAR and PN groups (Table 4) (p = 0.38). Intensive care unit stay was 2.9 ± 7.8 days (min: 1-max: 36) in the PAR group and 2.4 ± 6.8 days (min: 1-max: 60) in the PN group. There was no significant difference between the groups in terms of intensive care unit stay (p = 0.80). Since all patients were followed up in the intensive care unit on the postoperative 1st day, the patients were also studied for the ratio of the patients who stayed for 1 day and those who stayed for longer than 1 day, and no statistically significant difference was observed between the two groups (Table 4) (p = 0.82).

Table 4. Hospital stay and ICU stay as indicators of morbidity.

		PAR (n=20)	PN (n=88)	p
		Mean ± SD, range	Mean ± SD, range	
Hospital stay (days)		11.6 ± 7.9	12.3 ± 11.3	0.3
		n (%)	n (%)	
ICU stay (days)	stay for 1 day	17 (85)	73 (83)	0.8
	stay for longer than 1 day	3 (15)	15 (17)	

Abbrev.; ICU: intensive care unit, SD: standard deviation.

3. Mortality

In the PAR group, in one patient who could not be extubated in the postoperative period, hospital mortality occurred due to ventilator-associated pneumonia, ARDS, sepsis and multi-organ failure on the 28th day (5%). In the PN group, hospital mortality occurred in 5 patients (%5.6). Of these 5 hospital mortalities; 2 occurred on the 19th and 21st days due to sepsis and multi-organ failure following post-operative pneumonia, 1 occurred due to bronchopleural fistula and empyema on the 12th day, and the other 2 occurred due to cardiac and renal problems on the 16th and 24th days. When the groups were evaluated in terms of mortality rates; although there was a higher rate of mortality in PN group, no significant difference was determined (p > 0.05) (Table 5).

Table 5. Postoperative mortality.

Cause of death	PAR	PN
Pneumonia, ARDS	1	2
Broncho-pleural fistula		1
Myocardial infarction		1
Renal failure		1
Total (n, %)	1 (5)	5 (5.6)

Abbrev.; ARDS: adult respiratory distress syndrome.

4. Survival

The median follow-up period for all patients was 31.5 months (range: 0-84 months) and total 5-year survival was 56.2%. In November 2012, when the follow-up was terminated, 13 (65%) patients in the PAR group and 55 (62%) in the PN group were alive. The two groups were similar in terms of follow-up periods (p = 0.75). Overall 5-year survival results (59.8% and 56%, respectively) and mean survival time (58 and 54 months, respectively) were more advantageous in the PAR group

compared to the PN group (p = 0.81); however, this advantage was not statistically significant (Figure 1).

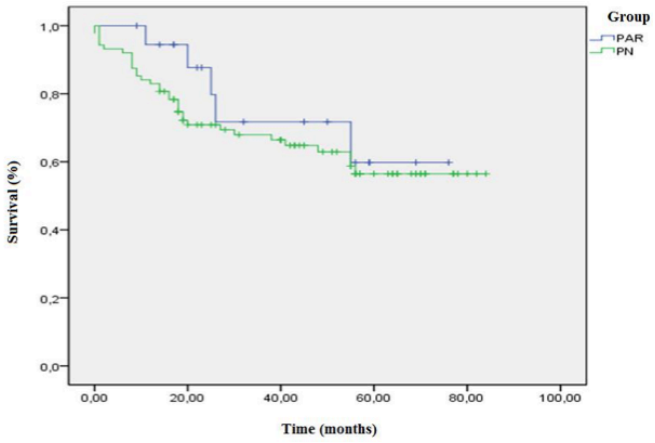

Figure 1. Comparison of survival between groups.

While total 5-year survival rates were similar in both groups in early-stage (stage I + II) tumors (p = 0.73), total 5-year survival in late-stage (stage III) tumors was observed to be significantly better in the PAR group (p = 0.04).

Discussion

If any cure could be offered for lung cancer, surgical resection is the most important treatment method today. Complete resection is associated with tumor recurrence and survival, and the amount of resected pulmonary tissue is associated with perioperative morbidity, mortality and quality of life [4,27,28].

Since pneumonectomy has high mortality and morbidity and decreases the patient's quality of life, parenchyma sparing bronchoplastic and angioplasty procedures have been defined [29,30]. If the tumor has invaded the pulmonary artery, the only alternative to pneumonectomy is the reconstruction of PA, no matter bronchoplasty is required or not. However, based on the results of the early publishments, this technique was thought to be laborious, time-consuming and associated with high mortality and morbidity rates [31]. Until Rendina et al. [17,32] had published many specific intraoperative techniques related to PA sleeve resection and their positive results, difficulties were encountered in the acceptance of PA reconstruction, and no real advance could be achieved. Furthermore, there were serious concerns about the probability of a high tumor recurrence risk, which would limit survival [33], and this technique was not adopted by many thoracic surgeons.

Due to the recently reported acceptable morbidity, mortality and long-term survival outcomes of PA resection and reconstruction concurrent with lobectomy, this technique has been accepted as an advantageous alternative to pneumonectomy [1,17,18,21,34]. In our study, the morbidity rates observed in PAR and PN groups were 30% and 53%, respectively. No significant difference was observed between the groups in terms of the incidence of morbidity. However, when bronchial morbidities were taken into consideration, statistically significantly higher BPF was identified in the PN group (p = 0.04). This showed us that in central lung tumors, pulmonary artery reconstruction concurrent with standard or sleeve lobectomy could be employed with lower peroperative risk compared to pneumonectomy.

In PAR group, no procedure-specific mortal complications such as dehiscence on the bronchial or vascular anastomosis site or broncho-vascular fistula were observed. It demonstrated the importance of covering the anastomosis site with living tissues such as the pleural or intercostal muscle flap, just as we did in our cases. In particular, it emphasized that the intercostal muscle flap prevents the development of bronchopleural fistula by providing airway continuity even if small dehiscences may occur in the anastomosis site. It has also been reported in the literature that many materials such as pericardium, pericardial fatty tissue, omentum, mediastinal pleura and azygos vein can be used for covering [22,24,26,34]. Besides, PA thrombosis is quite a rare complication [20,32], as supported by the literature, and should not be a concern about PAR. In our study, too, no symptoms of PA thrombosis or occlusion was observed in, and follow-up contrast-enhanced thorax CT revealed no signs of chronic PA obstruction or stricture.

In our study, the mean length of hospital stay in the PAR group was 11.6 days. In the literature, it is reported that the time of hospitalization of patients undergoing PAR is long [1,34]. Although, it was not statistically significant, the duration of hospital stay and duration of intensive care unit stay was found to be higher in PN patients. This may be indicative of physiological disadvantage due to decreased pulmonary reserve after PN.

In our study, hospital mortality was observed in one patient in the PAR group (5%) due to ARDS and sepsis secondary to pneumonia. Although there was no sig-

nificant difference in mortality between the groups in our study, it has been shown in the literature that parenchymal sparing surgeries could be performed with less mortality rate compared to PN, and the importance of spared pulmonary reserve has been emphasized [12,13,26,34]. Right-sided surgery is the major surgical risk factor in PN [35], however, in our study, most of the patients underwent left pneumonectomy, extended pneumonectomy cases were not included in the study, and the number of the patients in PAR group was low, so we believe that these are the reasons why the mortality rates of PN and PAR groups were similar.

Bronchoplastic procedures have been reported to be an acceptable alternative to PN in terms of survival and local recurrence and have been recommended to be performed whenever possible [10,12,13,24,26]. However, due to the need for complex surgical procedures in angioplasty procedures, the worry that a complete surgery cannot be achieved, and the expectation that local recurrence will increase and thus the survival will decrease, the adaptation of surgeons to this technique has been slow. The number of publications in which long-term survival outcomes of angioplasty procedures have been reported is relatively low in the literature [17-20]. The first 2-year and total 5-year survival results (69% and 59%, respectively) observed in our study are similar to or better than the results of these studies. However, mostly heterogeneous patient populations (tangential resection and original PAR) were analyzed in these studies, and survival results were often presented together with bronchial sleeve resections. Due to the number of patients, demographic characteristics, inclusion criteria, tumor stages, and the differences in the follow-up periods, it is difficult to compare the results obtained in other series with ours and to evaluate the oncological success of our angioplasty practices.

That the arterioplasty concomitant with bronchoplasty is oncologically superior to PN has been demonstrated in some comparative studies [1,19,20,24,26]. It has been reported that it is oncologically successful in the radical local control of the disease and has lower local recurrence rates. In a meta-analysis performed by Ma et al., [21] it was reported that the results of PAR and sleeve lobectomy were similar in terms of postoperative mortality, morbidity, 5-year survival, and local recurrence, and these results were better than PN. Besides, it was reported in that study that PAR application together with sleeve lobectomy is both technically and oncologically as safe as isolated sleeve lobectomy. It was emphasized that radical operations such as PN are not necessary even in higher-stage tumors.

In our study, the first-2-year disease-free survival results (69% and 64% respectively), total 5-year survival results (59% and 56% respectively) and the mean survival time were more advantageous in the PAR group than PN group, but this advantage was not statistically significant. We believe this is because the number of the patients in PAR was low, only the stage I-IIIA tumors were analyzed, and most of the patients in the study had stage II tumors. When the survival results in our study were analyzed according to the intergroup stages, the survival results in early-stage tumors (stage I+II) were found to be similar; however, the survival in PAR group was significantly better than PN group in stage III tumors (52% and 30% respectively). This shows us that even in more advanced stage tumors, more radical operations such as PN are not necessary to achieve a better survival. This may indicate that PN patients, even at the same stage, have a greater central tumor and more lymph node involvement, both of which affect the survival. Besides, no local recurrence was detected on the pulmonary artery suture line or bronchial anastomosis in any of the PAR patients. The possible reasons for this may be that PAR was applied only to the patients with R0, the patients in the study had relatively low stages and the follow-up period was shorter (median 26 months). However, since the majority of lung cancer recurrences occur within the first 2 years [36], it is not possible that our local recurrence rate would have increased dramatically if our follow-up period had been longer.

The main limitations of this study can be listed as follows; its retrospective design, the low number of patients in the PAR group, the heterogeneity in the tumor histology and stages, that the operations were performed by different surgeons, and the short follow-up period.

In conclusion, this study showed that to avoid pneumonectomy in central lung tumors, pulmonary artery reconstructions can safely be performed with acceptable morbidity and mortality rates. According to the comparison between the homogeneous patient groups, onco-

logic results of pulmonary angioplasty procedures were not worse than those of PN. The PAR group revealed that even in more advanced stage tumors, more radical operations such as PN are not necessary to achieve a better survival. In the light of these data; major anatomical lung resection with pulmonary angioplasty is a suitable procedure not only for patients who cannot tolerate pneumonectomy but also for all patients in whom this procedure is anatomically and oncologically feasible.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

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Current Thoracic Surgery

To cite this article: Dumanlı A, Elmas M. Investigation of clinical and genetic data of pectus excavatum in dysmorphological children: a single-center experience. Curr Thorac Surg 2020; 5(1): 10-15.

Original Article

Investigation of clinical and genetic data of pectus excavatum in dysmorphological children: a single-center experience

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ABSTRACT

Background: Pectus excavatum (PE) is one of the most common chest wall deformations. However, the pathogenesis of the disease is not completely understood and the results of the researches remain inconsistent. There are not enough studies in the literature investigating the most common anomalies accompanying PE. Thus, in this study, we aimed to evaluate the prenatal, natal, postnatal, genetic and clinical findings associated with congenital PE.

Materials and Methods: Eighteen patients with PE (10 males, 8 females) who admits Afyonkarahisar Health Sciences University were included in the study between 2012 and 2018. Patients were investigated clinically, radiologically and genetically to determine the etiology and risk factors of PE. PE is accompanied by several anomalies and has many systemic effects. The ages of the study patients who applied to the dysmorphology clinic and included in the study ranged between 0 and 18. The findings and genetic results of approximately 120 piece dysmorphological parameters of prenatal, natal and postnatal periods of PE patients were investigated.

Results: Five parameters associated with PE were recorded in this study, which include intrauterine growth retardation (IUGR), high Beighton score, hypotonia, cryptorchidism and microcephaly.

Conclusions: Treatment of PE requires a detailed and multidisciplinary approach.

Keywords: microcephaly, funnel chest, Noonan syndrome

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Doi: 10.26663/cts.2020.0002
Received 08.08.2019 accepted 23.09.2019

Introduction

In a patient with PE, the breastbone is sunken into his/her chest. In severe cases of pectus excavatum the chest can look as if carved, leaving a deep dent. PE, also called funnel chest, is more common in boys than girls are and severe cases can eventually interfere with heart and lung functions. There are several hypotheses regarding the pathogenesis of PE. In one of the first hypotheses, Bauhinus et al., mentioned that hypertension of the diaphragm during embryonic development could be a pathophysiologic factor. However, recent hypotheses focus on the defective sternocostal cartilage metabolism that results in biomechanical weakness and overgrowth of the sternocostal cartilage. A systematic histological analysis of the sternocostal cartilage of patients with PE has identified premature aging of the cartilage. An ultrastructural and biochemical study, which was designed to identify the reason for deterioration of sternal cartilage, revealed that the costal cartilage elements obtained from patients with PE were normal. The dietary zinc amount is correlated with the decreased metabolic activity of chondrocytes. Hence, in light of these findings there is a correlation between metabolic lesions and mechanical properties of sternal cartilages of patients with PE [1,2]. The most common chest wall deformities are PE and pectus carinatum which constitutes 95-97% of all chest wall deformities and some rare disorders such as cleft sternum, asphyxiating thoracic dystrophy (Jeune syndrome), pentalogy of Cantrell, spondylothoracic dysplasia (Jarcho–Levin syndrome) and Poland syndrome represent the remaining ~3–4% of the deformities [2]. PE is the most common chest wall deformity, which is caused by the dorsal deviation of the sternum and the 3rd to 7th rib, or costal cartilage that represents 90% of all chest wall deformities. Thoracic organ and spine deformities may be present depending on the severity of PE. Although in most cases, PE has little or no effect on the functions of underlying organs, the cosmetic appearance may produce psychological problems that require treatment. The main treatment of PE is by surgical intervention. There are several operative methods in the literature. There are several hypotheses regarding the pathogenesis of PE, however, the underlying mechanism is still not identified. There are questions about the role of developmental processes in the pathophysiology of PE [1].

Dysmorphology is the study of human congenital malformations and birth defects, particularly those that affect the morphology of individuals. This term describes the body (such as stature, hand, feet and neck) and the face characteristics (head shape, nose length, ear position, vermillion thickness, etc.) of individuals compared to the same age group and ethnicity. A genetic etiology should be suspected if a child has one or more of these dysmorphic features: Congenital anomalies, growth retardation, underdeveloped secondary sexual characteristics or ambiguous genitalia and developmental delay and/or intellectual disability and/or developmental regression [3].

Head circumference measurement is an indirect and simple method to determine the normal progression of brain growth, which provides information about the intracranial volume. Growth of head circumference is very important for the normal development of the brain [4].

Hypotonia is an impairment, which is associated with many different conditions regarding genetic neuromuscular, connective tissue, central nervous system, connective tissue, and/or metabolic origins [5]. Muscle tone is clinically assessed by evaluating the resistance to passive stretching, and a reduction in the muscle tonus is defined as hypotonia. Stiffness of the muscles, tendons and soft tissues, as well as muscle contraction, contributes to muscle tone. Voltage reflex mechanism pathologies and the reduction of the segmental motor neuron excitability have been suggested as the physiological etiology of hypotonia [5].

Cryptorchidism is the absence of one or both testes within the scrotum. The incidence of cryptorchidism is high and nearly 3% of boys are undergoing an operation for this disorder in the western countries. Cryptorchidism results from the abnormalities of the hypothalamo-pituitary-testicular axis it is present in almost all of the individuals with one testis and abnormal sexual characteristics [6].

The presence of a history of hypoxic birth is important. Hence, the APGAR score (calculated from the parameters of activity, pulse, grimace, appearance and respiration) of the patients is recorded. These patients are followed for a long term in the medical genetic clinics, particularly for the presence of hypotonia. The patients are classified in one of 3 categories according to the APGAR score; low (0-3), intermediate (4-6) or normal (7-10). A low APGAR score at birth is associated with increased risk of neurological diseases, such as cerebral palsy, cognitive disorders or epilepsy [7,8]. We aimed to evaluate the genetic and clinical findings associated with congenital PE. In this way, we tried to determine the risk factors accompanying PE.

A scoring method was developed by Carter and Wilkinson in 1964 to determine generalized joint hypermobility. Later in 1973, this scoring method was

modified by Beighton et al. Beighton Scoring, which we use today to determine generalized joint hypermobility, was defined. In this scoring system, the total scoring is between 0 and 9. If the total score is 5 or more, it is considered generalized joint hypermobility [9].

Materials and Methods

Written informed consent was obtained from all participants and their families and the study was performed under a protocol approved by the Afyon Kocatepe University Medical Ethics Committee (2018/9).

Eighteen patients (10 males and 8 females) were enrolled in the study between 2012 and 2018. The hospital records of the study patients were investigated for the presence of the anomalies related to PE. The hospital records of the patients were investigated from the prenatal period and fetal characteristics such as fetal movements, polyhydramnios, oligohydramnios, intrauterine growth retardation (IUGR) and the maternal diseases such as diabetes, hypertension, and preeclampsia were recorded.

Besides, the birth style, birth weight and time of birth were recorded and the reason for caesarian section was investigated if it was preferred as the birth style.

Statistical Analysis

The statistical analysis was performed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation while categorical data were expressed as numbers or percentages where appropriate. Chi-square test was used for the statistical comparison of two groups and a p-value less than 0.05 was accepted as statistically significant.

Results

The most common comorbidities were observed in patients with PE. IUGR was present in 4 out of 18 patients in the prenatal period. A diagnosis of IUGR was established at the mean 20th week of the pregnancy. The average birth weight of the study patients was 1980 gr.

In 3 patients, the 5th postpartum minute APGAR score was between 4-7 (mild hypoxic birth trauma). Two of the patients was and APGAR score of less than 4 (severe hypoxic-ischemic birth trauma). These patients were followed in the neonatal intensive care unit for the long term.

The head circumference of the study patients was recorded for 2 years after birth. Microcephaly was present in 3 of the patients at birth. The average head circumference of these 3 patients was 33 cm and these patients remained to have microcephaly when they were 2 years old.

Hypotonia was present in 2 of the study patients and cryptorchidism was detected in 2 of the 10 male patients both of which were bilateral.

It was also identified in our study that the mean Beighton scores were elevated. Six of the patients had high Beighton scores and the Beighton score of all patients was 5 or more.

The genetic tests revealed that; 2 patients had Marfan Syndrome, 2 patients had Ehler Danlos Syndrome type 1, 2 patient had Turner Syndrome, 2 patients had Rasopathies (1 BRAF mutation and 1 SOS1 mutation) (Figure 1), one patient had Fragile X syndrome, one patient had Sotos syndrome, one patient had Digeorge Syndrome and one patient had mucopolysaccharidosis (MPS) type 4a (Morqiuo Syndrome) (Figure 2).

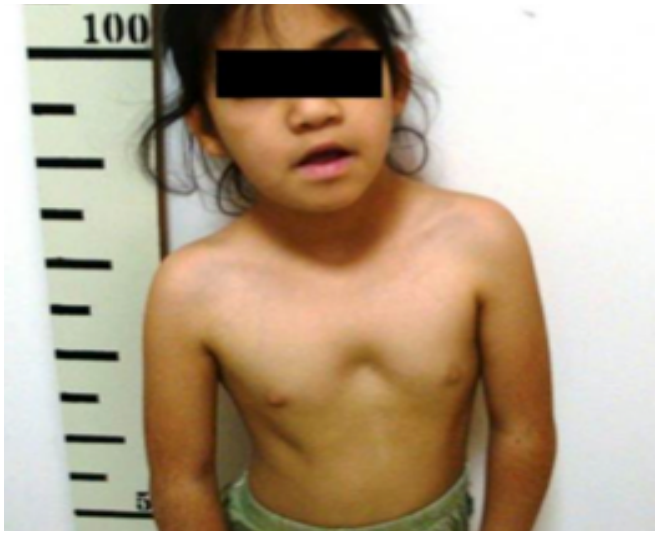

Figure 1. Noonan Syndrome

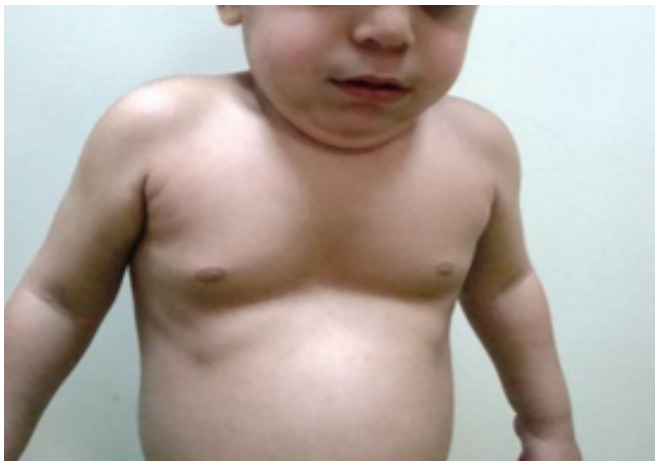

Figure 2. Morqiou Syndrome

Dysmorphıc Facıal Features are shown in Table 1 and the clinical and genetic results of the patients are shown in Table 2.

Table 1. Dysmorphic facial features.

Case ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Anteverted nares										+		+						
Attached lobe															+			
Bilateral ptosis													+					
Brachycephaly	+					+	+	+	+	+	+			+				
Broad chin						+	+	+	+			+						
Broad columella		+	+	+	+			+	+	+			+					
Broad eyebrow								+										
Broad face														+				
Broad forehead				+														
Broad jaw				+								+		+				
Broad nasal tip								+	+	+								
Broad philtrum				+														
Bulbose nose										+			+					
Coarse face								+						+				
Deep philitrum		+	+															
Deep set eyes	+							+	+									
Enlarges nares	+				+													
Epicanthus												+					+	
Everted antitragus											+	+						
Flat face																	+	
Flat occiput	+					+					+							
Full checks				+					+		+		+	+	+			
Hypertelorism					+		+	+	+	+	+	+		+	+		+	+
Hypotelorism		+	+															
Infra-orbital fold		+	+						+									
Large lobe								+	+									
Large nose								+	+									
Long ear				+				+	+	+								
Long eyelashes															+		+	
Long face										+								+
Long nose							+		+									
Low-set ears		+	+				+	+				+			+			
Macrotia					+			+	+									
Malar flattening	+									+		+	+		+			
Malar prominence		+	+					+	+									
Microcephaly														+				
Midface retrusion																	+	
Narrow forehead	+					+									+		+	+
Narrow jaw										+							+	+
Pointed chin	+									+	+		+					+
Premaxillary										+								
Prognathism														+				
Prominence										+								
Protruding ear								+	+		+	+						
Round face														+				
Short chin									+									
Short columella												+						
Short philitrum							+		+									
Sloping forehead	+																	
Small lobe										+			+					
Smooth philtrum				+												+		
Sparse eyebrow		+	+															+
Square face	+	+	+	+			+		+			+						
Synophrys				+													+	
Tall chin															+			+
Telecanthus	+			+	+		+		+	+	+	+	+	+	+			+
Tented philtrum									+									
Thick eyebrows	+												+	+	+		+	
Triangular face						+											+	
Wide mouth									+									
Wide nasal base		+				+		+	+	+								
Wide nasal bridge	+			+	+	+		+	+	+		+	+					
Wide nasal ridge	+				+			+	+	+			+					
Widow's peak		+	+															

Table 2. Clinical and genetic results of the patients.

Case ID	Gender	Cardiac examination	Genetic test result
1	Female	Mitral valve prolapse, aortic root dilatation	FBN1 c.4096G>A
2	Female	Aortic root dilatation, MVP	FBN1 c.5030A>G
3	Male	Mitral valve prolapse	COL5A1 c.1186G>C
4	Male	Normal	COL5A1 c.4916G>C
5	Male	Tetralogy of Fallot	22q11 microdeletion
6	Female	Patent foramen ovale	None
7	Male	Patent foramen ovale	BRAF:c.736G>C
8	Male	Pulmonary stenosis	SOS1 c.1656G>C
9	Male	Pulmonary stenosis	None
10	Male	Patent foramen ovale	None
11	Female	Bicuspit aortic valve	45XO
12	Male	Mitral insufficiency	GALNS c.1460A>G
13	Female	Tricuspid insufficiency + mitral insufficiency	45XO
14	Female	Atrial septal defect	NSD1 c.5908_5911delGAGT) Heterozygote
15	Male	Patent foramen ovale	FMR1 CGG 200>repeat
16	Male	Ventricular septal defect, Atrial septal defect	47XY+21Down syndrome
17	Female	Normal	None
18	Female	Normal	None

Discussion

It was previously reported that patients with PE have biochemical and histopathological abnormalities in the costal cartilage and the patients affected from PE show varying degrees of loose connective tissue [7]. In accordance with that, all of our study patients had genetic syndromes that affect the skeletal system.

There was no similar article in the literature investigating our clinical data. Therefore, it is difficult to compare our results with the literature.

Marfan Syndrome and Marfanoid properties were present in approximately 15% of the patients. It is known that Marfan Syndrome is associated with pectus excavatum, scoliosis, aortic dilatation and lens dislocation. Patients with Marfan Syndrome had more severe PE. Marfan Syndrome was present in two of our patients.

In their study, Nuss et al., reported two sisters and a younger brother with severe PE. The frequency of familial pectus excavatum is 40% [2]. In our study, 5 of the patients had a definite genetic etiology.

In cases with mucopolysaccharidosis (MPS), PE is observed due to "dysostosis multiplex" which is a quite specific radiological expression. In most of the MPS disorders, skeletal abnormalities are early and prominent features and the degree of skeletal involvement varies between MPS subtypes. Most patients have radiographic dysostosis multiplex, which includes PE, abnormally shaped vertebrae and ribs, spatulate ribs, enlarged skull, bullet-shaped metacarpals, hypoplastic epiphyses, and thickened diaphyses. Thoracolumbar kyphosis or gibbus deformity are often present and important in the diagnosis [8].

In conclusion, the cases of PE show genetic and clinical heterogeneity as seen in our study. Therefore, the approach to the patients should begin with a detailed anamnesis. Genetic inquiry and research should be done in detail. Parental consanguinity marriage and the presence of PE in the family members should be questioned. Afterward, a detailed physical examination and radiological imaging should be performed. The approach to the patients should be multidisciplinary and holistic. With the development of technology, diagnosis of molecular diseases has become easier. However, the importance of obtaining a detailed anamnesis and clinical examination is still important. Therefore, no matter how far technology progresses, the multidisciplinary and holistic approach to the patients will always be important. Multidisciplinary evaluation is very important in rare diseases such as PE.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

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Current Thoracic Surgery

To cite this article: Ceritoğlu A, Sezen CB, Aker C, Girgin O, Akın H. Prognostic factors associated with morbidity and mortality after surgery for postintubation tracheal stenosis. Curr Thorac Surg 2020; 5(1): 16-22.

Original Article

Prognostic factors associated with morbidity and mortality after surgery for postintubation tracheal stenosis

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ABSTRACT

Background: In this study, we reviewed the treatment, follow-up, and prognostic factors associated with complications in patients who underwent tracheal resection due to postintubation tracheal stenosis (PETS), in light of the literature.

Materials and Methods: Twenty-five patients who were operated for PETS between June 2012 and June 2017 were retrospectively evaluated. The patients' postoperative complications and prognostic factors affecting mortality were examined.

Results: There was 11 female (44%) and 14 male (56%) patients. Eight patients (32%) had comorbidities. The mean prolonged intubation time was 47.4 ± 55.0 minutes. Eight patients (32%) developed postoperative morbidity. The main prognostic factors associated with morbidity were the length of the stenotic area and the presence of endocrine and respiratory comorbidities ($p<0.05$). Tracheal fistulae were observed in 2 patients. The postoperative mortality rate was 8% (n=2). One patient with fistula died on postoperative day 2, while another patient died at postoperative three months due to cardiac failure. No significant factor was identified in relation to the development of tracheal fistulae.

Conclusions: The most important factor associated with complications was the presence of endocrine comorbidities. Although tracheal surgery results in high rates of postoperative morbidity and mortality, we believe these risks can be reduced by experienced surgeons and appropriate patient selection.

Keywords: tracheal stenosis, postintubation, surgery

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Doi: 10.26663/cts.2020.0003
Received 07.08.2019 accepted 14.10.2019

Introduction

In addition to surgical treatment for postintubation tracheal stenosis (PETS), methods such as bronchoscopic dilatation, laser ablation, and stent placement are also available. Reports have indicated that bronchoscopy can be curative in many selected cases [1-3]. Mehta et al. reported that diaphragm- or web-like stenoses could be treated by mucosal separation technique with a success rate of 60% after 1–3 sessions [4]. However, mechanical dilation alone in cases of long or inoperable stenoses leads to more than 90% recurrence [1].

To date, there have been few publications regarding tracheal resection due to PETS. In particular, there is not enough literature on this subject in Turkey. There have also been very few studies investigating the prognostic factors associated with anastomotic complications.

In this study, we review the treatment options, follow-up, and prognostic factors that may lead to complications in patients who undergo tracheal resection due to PETS, in light of the literature.

Materials and Methods

Data pertaining to patients operated for PETS between June 2012 and June 2017 were retrospectively evaluated from a routine patient database. Twenty-six PETS patients were initially evaluated for the study. One patient was excluded due to a lack of follow-up. The study included 25 patients, 11 females (44%) and 14 males (56%), who underwent tracheal resection and end-to-end anastomosis due to PETS. This study was approved by the institutional review board of İstanbul Education and Research Hospital (2017/1035) and was conducted in accordance with the principles of the Declaration of Helsinki.

Preoperative Evaluation

Fiberoptic bronchoscopy was performed on each patient to determine the location and size of the tracheal lesion. Rigid bronchoscopy was performed to perform dilation in patients with severe respiratory distress. In addition to bronchoscopy, cervical computed tomography was used on all patients to determine the location of the lesion and the relationship of the trachea with adjacent structures. An esophagography was requested in addition to bronchoscopy from one patient because they had a tracheoesophageal fistula in addition to tracheal stenosis.

Preoperative comorbidities were classified into three groups: endocrine diseases (diabetes), cardiac problems (hypertension, heart failure, and coronary artery disease), and respiratory conditions (asthma and chronic obstructive lung disease).

Surgical Technique

All patients were evaluated on the operating table by rigid bronchoscopy. To mark the proximal edge of the stenosis, the anterior trachea was pierced with a sterile needle as the patient lay in a supine position. The patients were intubated with a spiral intubation tube (number 6-7) based on stenosis severity. Patients with stenoses too narrow to be intubated underwent dilatation with rigid bronchoscopy on the operating table before intubation.

Operations were performed using the technique described by Pearson and Grillo [5,6]. The neck was positioned in hyperextension, and a collar incision was made. The trachea was freed from the surrounding tissues while preserving the vascular supply and avoiding unnecessary dissection proximal and distal to the stenosis as much as possible.

Healthy tissue was cut horizontally from the inferior lesion margin. A sling suture with 2/0 polyglactin was placed in the distal trachea to prevent the trachea from moving distally when the horizontal incision was made. In general, horizontal incisions were made more proximally and even in the middle of the stenotic segment instead of at the far distal aspect of the lesion. Thus, the proximal and distal borders of the stenosis were also visible from within the lumen. Therefore, the stenotic segment was usually sent for pathological examination as two pieces, the distal and proximal portions. The intubation tube was removed proximally. It was noted that in cases of subglottic and proximal tracheal stenoses, the intubation tube moved proximally to the vocal cords during retraction, which made it difficult to reposition the intubation tube distally during anastomosis. To prevent this, a fixation stitch with 0 silk suture was placed at the end of the intubation tube. This allowed the tube to be positioned by pulling distally instead of pushing

through the mouth. The distal trachea was intubated with a second spiral tube that was connected to a ventilator via a sterile circuit brought into the surgical field.

The stenotic area was removed by circular resection at the upper and lower borders of the lesion (Figure 1).

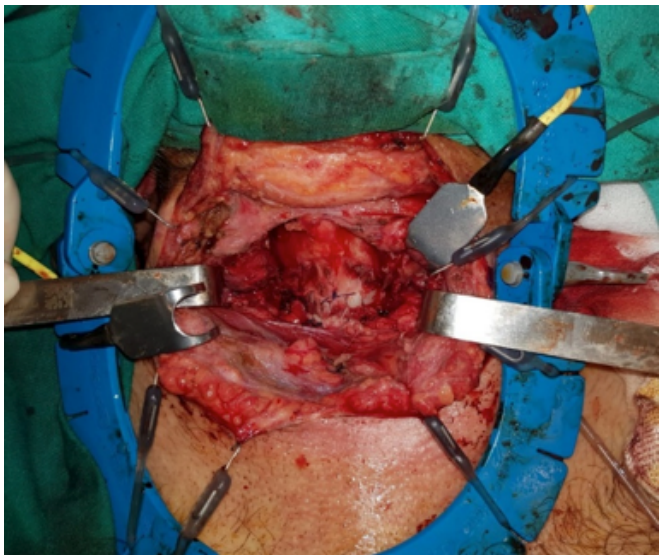

Figure 1. Intraoperative view after resection of the tracheal stenotic area.

Support sutures with 2-0 polyglactin were placed at the upper and lower ends of the trachea. The anastomosis was started from the posterior wall. The anastomosis of the posterior membranous wall was completed with interrupted or continuous stitches with 3-0 or 4-0 polyglactin or polydioxanone (PDS) suture. The anterior and lateral walls were also anastomosed with 3-0 or 4-0 polyglactin, or PDS interrupted sutures (Figure 2). Two jaw sutures were placed to prevent postoperative neck extension. These sutures were removed on postoperative day 7.

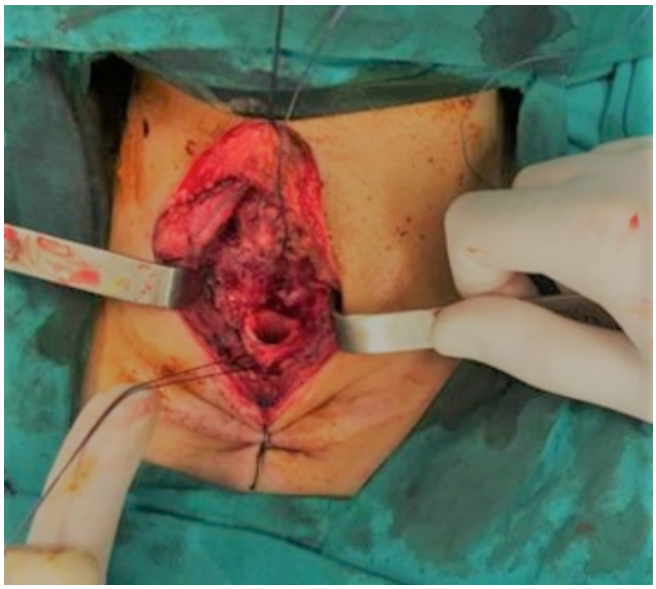

Figure 2. Intraoperative appearance after tracheal surgery.

Postoperative Follow-up

Postoperative morbidities were evaluated as complications that occurred in a hospital or during the first 30 days. Postoperative fistulae, hoarseness, superficial surgical site infections, deep surgical site infections, and hemorrhages were accepted as morbidities. Postoperative mortality was defined as deaths that occurred in a hospital or during the first 30 days.

Statistical Analysis

Statistical analysis of the study was performed with SPSS version 22 (Statistical Program for Social Sciences) software package. Descriptive statistics pertaining to categorical variables were expressed as frequencies and percentages, while those of continuous variables were expressed as mean, standard deviation, median, and minimum and maximum values. The Mann–Whitney U test was used to compare means between groups, and the chi-square test was used for comparisons of categorical variables. For all statistical comparisons, p values below 0.05 were considered statistically significant.

Results

Of the 25 patients included in the study, 14 were male, and 11 were female. Their mean age was 41.7 ± 16.81 (17-76) years. Comorbidities were present in 8 (32%) of the patients. The patients' demographic characteristics are shown in Table 1. PETS developed postoperatively in 11 patients (44%), due to respiratory arrest in 5 patients (20%), due to cardiac arrest in 4 patients (16%), and due to prolonged intubation for neurological reasons in 5 patients (20%). The mean prolonged intubation time was 47.4 ± 55.0 hours.

Table 1. Demographic characteristics of the patients.

Variable		n	%
Gender	Male	14	56
	Female	11	44
Age (years)	Mean ± SD	41.7 ± 16.81	
	<65	23	92
	>65	2	8
Comorbidities		8	32
Comorbidity	Cardiac conditions	4	16
	Respiratory conditions	3	12
	Endocrine conditions	5	20

Eight patients had a history of tracheostomy due to prolonged intubation. Three patients had tracheostomy at the time of surgery, while five patients had surgical scars from the previous tracheostomy. The average time to onset of postintubation symptoms in our patients was 12 months. All of the patients complained of dyspnea. Bronchoscopic examinations revealed that the distance between the level of stenosis and the vocal cords ranged from 1 to 4 cm. In one patient, the stenosis was 1.5 cm proximal to the tracheal carina. Twenty-four patients underwent a collar incision, while the patient with stenosis proximal to the tracheal carina underwent thoracotomy. The mean resection length was 3.19 cm. Resection length was 2.4-3 cm in 10 patients, 3-4 cm in 12 patients, and 4 cm or longer in 3 patients. The mean length of tracheal stenosis was 3.2 ± 0.67 cm.

Fifteen patients (60%) underwent a mean of 1.60 ± 0.73 (1-3) preoperative dilatations. Three patients (12%) who had surgery for PETS at another center were reoperated due to restenosis. Of these three patients, one had undergone laryngeal release in the previous surgery. This patient had a stenotic segment of 4.5 cm, and resection of 5.5 cm was performed. In another patient, esophagoscopic and bronchoscopic examination confirmed the persistence of the tracheal stenosis and tracheoesophageal fistula for which they underwent surgery previously. Simultaneous tracheal resection and tracheoesophageal fistula repair were performed. The third patient was reoperated due to the development of granulation tissue on the anastomosis made 3 cm from the vocal cords.

A total of 8 patients (32%) developed morbidities: tracheal fistulae in 3 patients (12%), hoarseness in 6 patients (24%), hemorrhage in 4 patients, deep surgical site infections in 3 patients, and superficial surgical site infections in 3 patients. Emergency tracheostomy was performed due to respiratory failure in 1 patient who developed hemorrhage. One patient underwent emergency tracheostomy in the early postoperative period due to bilateral recurrent damage. Complications occurred in 2 (66.6%) of the three patients who underwent repeat tracheal resection and in 6 (27.3%) of the 22 patients who were operated for the first time (p = 0.231). Factors associated with postoperative morbidity were having diabetes or respiratory problems as comorbidity. Prognostic factors associated with complications are shown in Table 2.

Table 2. Evaluation of factors associated with morbidity.

Variable		Morbidity(–) n (%)	Morbidity(+) n (%)	p
Gender	Male	11 (78.6)	3 (21.4)	0.389
	Female	6 (54.5)	5 (45.5)	
Age (years) Mean ± SD		39.2 ± 15.2	47.0 ± 19.7	0.440
Age (years)	<65	16 (72.7)	6 (27.3)	0.231
	>65	1 (33.3)	2 (66.7)	
Comorbidity		1 (12.5)	7 (87.5)	<0.001
Comorbidity	Cardiac conditions	1 (25)	3 (75)	0.810
	Endocrine conditions	1 (20)	4 (80)	0.023
	Respiratory conditions	0	3 (100)	0.024
Stenosis length (cm) Mean ± SD		2.95 ± 0.40	3.73 ± 0.83	0.006
Presence of tracheostomy		5 (62.5)	3 (37.5)	0.686

Two patients with tracheal fistulae underwent a permanent tracheostomy. Fistula-related mortality occurred in 1 patient. No factor was statistically associated with the formation of tracheal fistulae in the study (Table 3). Polyglactin and PDS sutures were used in all patients in this study. For the membranous part, polyglactin was used in 3 patients (12%), while PDS was used in 88%. For anterior wall anastomosis, polyglactin was used in 8 patients (32%), and PDS was used in 17 (68%). In terms of anastomosis technique, interrupted sutures were used in the anterior wall in all patients. In the membranous wall, interrupted sutures were used in 9 patients and continuous sutures in 16 patients.

Table 3. Prognostic factors of tracheal fistula.

Variable		Fistula (–) n (%)	Fistula (+) n (%)	p
Gender	Male	12 (85.7)	2 (14.3)	1
	Female	10 (90)	1 (9.1)	
Age (years)		39.7 ± 16.0	56.6 ± 17.2	0.238
Age (years)	<60	20 (90.9)	2 (9.1)	0.330
	>60	2 (66.7)	1 (33.3)	
Comorbidity	Cardiac conditions	3 (75)	1 (25)	0.422
	Endocrine conditions	3 (60)	2 (40)	0.091
	Respiratory conditions	2 (66.7)	1 (33.3)	0.330
Stenosis length (cm) Mean ± SD		3.21 ± 0.70	3.13 ± 0.32	0.906
Dilation		12 (80)	2 (20)	0.250
Tracheostomy		8 (100)	0	0.527

Postoperative recurrence occurred in 3 patients. Two patients developed granulation tissue at the anastomosis site after two months and 18 months, and the stenosis was resolved with cryotherapy. Emergency tracheostomy was performed on one patient who presented with dyspnea at three months.

The postoperative mortality rate was 8% (n=2). One patient with fistula died on postoperative day 2, while another patient died due to cardiac failure at postoperative three months.

Discussion

Prolonged intubation may result in stenosis at different levels of the trachea. Stenosis can occur anywhere in the glottic and subglottic areas, depending on the level of the endotracheal intubation tube. It occurs most commonly where the endotracheal tube cuff comes into contact with the tracheal wall [7,8]. PETS is seen in 0.1-20% of patients with chronic intubation [9]. A much smaller proportion of these becomes clinically significant stenosis [10]. Patients generally seek medical attention when the stenosis occludes about 70% of the normal tracheal lumen. For this reason, mild stenoses are not detected.

Surgical treatment is considered for a small number of symptomatic patients. In their series, Grillo and Pearson also reported stridor and exertional dyspnea as important signs of stenosis in patients with PETS [5,6]. In the literature, the average length of PETS is reported as 2.6 cm [11]. In our series, all patients had complaints of dyspnea and stridor. The mean length of PETS was 3.2 ± 0.67 cm, similar to the literature.

Surgery is contraindicated, at least temporarily, in patients with poor general condition or unstable concomitant disease. Therefore, treatments, including bronchoscopic dilation, laser, and stenting, are recommended as an alternative to surgery [1,12]. Grillo et al. reported in a 1995 study that laser treatment was unsuccessful in 23-43% of cases and that conservative approaches can only be successful in selected patients [13]. In the present study, we observed that although bronchoscopic dilation is not an effective treatment, it is an effective method of gaining time until surgery and determining the length of the lesion by advancing the scope to the distal border of the stenotic segment. Of the 25 patients operated in our hospital, 15 (60%) had previously undergone dilation. These patients exhibited restenosis after the dilation procedure. Segmental tracheal resection and end-to-end anastomosis are the most effective methods for patients with PETS.

Although it may vary depending on stenosis location, the primary approach in cases of benign tracheal stenosis should be cervical incision and collar incision. Rarely, partial sternotomy can be performed if necessary. In a 589-case series published in 2004, Wright et al. reported using cervical, mediastinal, and thoracic incisions in 79.6%, 20%, and 0.5% of their patients, respectively [15]. In the present study, a cervical incision was used in all cases except a 76-year-old patient with stenosis 1.5 cm proximal to the tracheal carina. In order to minimize complications, curative surgery is only recommended for selected patients with good neurological, cardiovascular, and respiratory status. The basic principles for avoiding complications have been

determined to be reducing the tensile force on the anastomosis, not disrupting the vasculature, and practicing meticulous dissection [16]. Release techniques are used to reduce the tensile force on anastomoses. Although the resection limit was 2 cm in early studies, this limit was increased up to 6.5 cm with the development of release techniques [14]. When we compared resection length and complication rates in the present study, the length of 3.73 cm in the group with complications and 2.95 cm in the group without complications was statistically significant, as expected ($p = 0.006$). The mean length of the resected segment was 3.13 cm in the three patients with fistulae, while this length was 3.21 cm in patients without fistulae ($p = 0.906$). We attribute the discrepancy between our results and those in the literature to our small patient group.

Release techniques include right hilar release, suprahyoid and laryngeal release, pulmonary ligament dissection, intrapericardial dissection of pulmonary vessels, reimplantation of the left main bronchus to the intermediary bronchus, and head flexion. Wynn et al. preferred supralaryngeal release to avoid postoperative dysphagia and reported a success rate of 89% [15]. All of these release techniques reduce tension on the anastomosis line as well as prevent surgical site separation and granulation, restenosis, and surgical site infection. Laryngeal release techniques were not used in any of the 25 patients in the present study.

Diabetes is an important predisposing factor for anastomotic complications. It increases the complication rate by 3% [16,17]. When we evaluated complication rates in terms of diabetes mellitus, various complications were observed in 4 of the five diabetic patients ($p = 0.023$). Microcirculation is known to be impaired in diabetic patients. Disruptions in collateral circulation are seen on the anastomosis line, which adversely affects tissue healing. Separation at the anastomosis line has been observed in 22% of diabetic patients [18]. Two of the three patients with fistulae in our study were diabetic ($p = 0.091$).

Another patient group with impaired microcirculation is patients undergoing revision surgery. We encountered complications in 2 of our three previously operated patients ($p = 0.231$), though these complications were surgical site infection and hoarseness. Although fistula was not observed, the rate of anastomotic complications is higher in these patients due to impaired collateral circulation.

Another important issue related to the development of complications is comorbidities [7]. In the present study, comorbidities were found to be associated with complication development ($p = 0.024$). One of our patients was died because of self-extubation after the operation. Self-extubation was damage the anastomosis. Therefore, comorbidities must be taken into account during patient selection. We believe that patient compliance is a more important criterion for patient selection than the length of the stenotic trachea.

As described by Grillo and Pearson, anastomosis of the posterior wall is done first with interrupted sutures; then the cartilage part is approximated with interrupted sutures [13,19]. Macchiarini used the continuous suture technique on the posterior wall and reported a restenosis rate of 7.6% [20]. Wynn et al. used the posterior and anterior interrupted anastomosis technique described by Grillo and Pearson and reported 11% restenosis [15]. In the present study, polyglactin and PDS sutures were used in all patients. The ratio of polyglactin to PDS use was 12%/88% for the membranous part and 32%/68% for anterior wall anastomosis, respectively. As the anastomosis technique; interrupted sutures were used in the anterior wall in all patients, while the ratio of interrupted to continuous suture use in the membranous wall was 36%/64%, respectively.

Anastomotic complications are detected during routine bronchoscopic examinations [21]. Wright et al. stated that the best option for the treatment of restenosis is the T-tube or tracheostomy tube because it does not impair airway humidification and allows phonation [17]. In the present study, repeated bronchoscopy and laser ablation were performed on two patients with granulation. One patient with restenosis underwent a permanent tracheostomy.

The limitations of the study are the retrospective design and the fact that the patients' preoperative general condition could not be evaluated, and their operations were performed by different surgeons may create bias in our study.

In conclusion, while we were not able to identify risk factors for fistulae due to the small number of patients in our study, we determined that comorbidities were the most important factor affecting postoperative complications. Although tracheal surgery is associated with high

postoperative morbidity and mortality, we believe these risks can be reduced with experienced surgeons and appropriate patient selection.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

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To cite this article: Yazicioglu A, Uysal S, Senat A, Sahinoglu T, Sahin MF, Biçer C, Erel Ö, Yekeler E. Does sericin pleurodesis increase the basic fibroblastic growth factor and high-sensitive C-reactive protein levels in rat plasma? Curr Thorac Surg 2020; 5(1): 23-30.

Original Article

Does sericin pleurodesis increase the basic fibroblastic growth factor and high-sensitive C-reactive protein levels in rat plasma?

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ABSTRACT

Background: This study investigates whether or not sericin pleurodesis increases basic fibroblastic growth factor (bFGF) and high-sensitive C-reactive protein (hs-CRP) levels in rat plasma.

Materials and Methods: A total of 42 adults, male, 12-week-old Wistar albino rats were obtained for the study. The rats were divided randomly into three groups, as sericin, talcum powder, and control group. After the administration of an anesthetic, the agents were administrated through a left thoracotomy. The rats were sacrificed 12 days later through cardiac puncture. The bFGF and hs-CRP levels were examined in plasma.

Results: The mean rat plasma bFGF levels were 251.7 pg/mL in the sericin group (range: 101 to 821 pg/mL), 72.3 pg/mL in the talcum powder group (range: 24 to 131 pg/mL), and 133.1 pg/mL in the control group (range: 32 to 320 pg/mL). A significant difference was noted in the results of a Scheffe test between the sericin and talcum powder groups ($p < 0.05$, $p = 0.046$). Mean rat plasma hs-CRP levels were 1.038 ng/mL in the sericin group (range: 0.677 to 2.815 ng/mL), 1.343 ng/mL in the talcum powder group (range: 0.606 to 5.662 ng/mL), and 0.945 ng/mL in the control group (range: 0.586 to 1.261 ng/mL), indicating no significant difference among the groups.

Conclusions: It was found that bFGF levels were significantly higher in the sericin pleurodesis group than in the talcum powder group, indicating the biochemical success of intrapleural sericin administration in inducing pleurodesis. On the other hand, hs-CRP, a marker of inflammation, was not found to be significant, indicating that hs-CRP returns to normal levels due to its short half-life.

Keywords: sericin, fibroblast, fibrosis, growth factor, C-reactive protein, pleurodesis

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Doi: 10.26663/cts.2020.0004
Received 27.08.2019 accepted 04.11.2019
This abstract has been presented as a poster session in the American Thoracic Society, 2019 Conference, which was held at Dallas, Texas, United States of America, between 17 and 21 May, 2019.

Introduction

The cocoon shell of silkworms, Bombyx mori, is composed of two natural proteins, called fibroin and sericin [1,2]. Sericin is a natural, macromolecular, gum-like protein that holds fibroin polymers together, and is a by-product of the textile sector [1]. Previous studies have shown the pleurodesis success of sericin powder [3,4]. Yazicioglu et al. in an experimental study involving rats, concluded that the intrapleural administration of sericin increased fibroblastic activity and fibrosis in the visceral pleura, with no significant adverse effects on lung parenchyma [3]. Besides, no foreign body reactions were noted and there was no evidence of biological glue on the specimens in the sericin pleurodesis group. Furthermore, the rats in the sericin pleurodesis group had lower inflammatory reactions, than the control group [3]. In another study involving rats, Yazicioglu et al. compared sericin pleurodesis with talcum powder, doxycycline, and silver nitrate pleurodesis, and found that sericin pleurodesis was found to be better tolerated, the success of sericin pleurodesis was demonstrated, and the highest level of dense collagen fibers was noted in the sericin group [4]. Compared to the other agents, sericin displayed significantly greater protective characteristics on lung parenchyma and a lower potential for inflammation than the other agents [4]. Additionally, side effects concerning the kidneys and the heart were significantly lower in the sericin group than in the other groups, which led the authors to conclude that the sericin powder is a better-tolerated, more cost-effective agent, associated with fewer side effects and offering superior protection of the lung parenchyma, offering more effective pleurodesis [4].

These histopathological studies demonstrate a sericin-induced increase in the fibroblastic activity that leads to fibrosis, although the levels of basic fibroblastic growth factor (b-FGF), a serum marker of fibroblastic activity, are unknown. Similarly, the effect of the intrapleural administration of sericin on the high-sensitive C-reactive protein (hs-CRP) level is also unknown. If sericin is effective in inducing pleurodesis, b-FGF and hs-CRP levels can be expected to increase in rat serum, although there is only limited data in the literature related to this subject [5-7].

Although many agents have been used to achieve pleurodesis, talcum powder appears to be the most commonly used agent around the world [8]. In the present study, we investigated whether or not sericin pleurodesis increased the basic fibroblastic growth factor (bFGF) and high-sensitive C-reactive protein (hs-CRP) levels in rat plasma.

Materials and Methods

The rat model was selected due to the presence of a valid laboratory license, technical feasibility, and similar physiological characteristics when compared with humans. The sericin powder is commercially available and was purchased from Xi'an Lyphar Biotech Co, LTD, Xi'an, China; the talcum powder was purchase from Novatech SA (Steritalc®), Marseille, France.

It was critically important to determine the appropriate dose of administration of the agents used in this study. The studies previously conducted by Yazicioglu et al. used 30 mg sericin in rats and obtained successful results, and so we used the same dose of sericin in the present study [3,4]. The administrated dose of talcum powder in adults varied between 4 and 5 grams in previous studies, and so a dose of 17 mg was estimated to be appropriate for rats with a mean weight of 250 ± 30 g [9-11]. The study previously conducted by Yazicioglu et al. did the sacrification of rats 12 days later, and so we sacrificed them on the same day [4].

Animals

This experimental study received approval from the Ethics Committee of Kobay AS (Protocol Number-2018/291). A total of 42 adult male 12-week-old Wistar albino rats weighing between 234 and 310 g were used in the study. The rats were divided randomly and equally into three groups: the sericin group, the talcum powder group, and the control group. Each group comprised of fourteen animals. All the animals received humane care in accordance with the Turkish Government Animal Protection and Management Law.

Technique

The sericin powder was divided into 30-mg packs, while the talcum powder was divided into 17-mg packs and added to Eppendorf tubes. The rats were anesthetized using intramuscular injections of 5-mg/kg xylasine hydrochloride (Alfasan International B.V., Woerden, Holland) and 45-mg/kg ketamine hydrochloride (Richter Pharma A.G., Wels, Austria). Subsequently, the left hemithorax was shaved, skin preparation was performed with povidone-iodine solution, and the rats

were placed in the lateral decubitus position. A left thoracotomy incision (2-cm skin incision) was performed at the midsection between the spine and sternum. The muscles were bluntly dissected to allow exposure of the parietal pleura. Under direct inspection, the parietal pleura was opened, and 30-mg sericin powder was administrated into the pleural space of each rat in the sericin group (n = 14). In the talcum powder group, 17-mg talcum powder was administrated into the pleural space of each rat (n = 14). The remaining rats were allocated to the sham thoracotomy group. Subsequently, the muscle layers were sutured using the running suture technique with 3-0 coated and braided polyglycolic acid (Vicryl 3-0; Dogsan, Trabzon, Turkey). The skin incision was closed with 4-0 coated and braided polyglycolic acid (Vicryl 4-0; Dogsan, Trabzon, Turkey) using interrupted suturing technique. The pneumothorax was drained using a 20-gauge plastic catheter connected to a syringe applying negative pressure. The catheter was removed immediately after the closure of the thoracotomy. Subsequently, terramycin wound spray (oxytetracycline HCl with a blue marker dye) was applied to the skin incision. All the rats were weighed before surgery and before scarification, and the respective body weights were recorded.

After the operation, the rats were housed in individual stainless steel cages and closely monitored for any clinical evidence of pain or other abnormalities, such as vocalization, tachypnea, or restlessness. No analgesic drugs were added to food and water. The room temperature was kept at 21^0C (± 2^0C), the relative humidity was approximately 60% (± 10%), and the rats remained under simulated daylight conditions. The rats were given ad-libitum access to food and water. The rats were sacrificed on postoperative day 12, through a cardiac puncture. Blood samples of approximately 8-10 mL were taken slowly from the ventricle of the heart of each rat to avoid cardiac collapse.

Biochemical evaluation

The blood samples were placed in tubes containing ethylenediaminetetraacetic acid (EDTA), and plasma samples were separated from the cells through centrifugation at 1800 g for 10 min (Hettich Universal, 320 R, and Zentrifugen). The plasma samples were subsequently separated from the cells and added to the Eppendorf tubes. The tubes were stored at -80°C until the time of analysis. The biochemistry specialists (investigators AS, CK, and OE) were kept blind to the study groups.

Rat b-FGF/FGF2 enzyme-linked immunosorbent assay (ELISA) and rat hs-CRP ELISA kits were supplied by Elabscience®-USA. The methodology used in the study was based on the manufacturer's instructions.

Statistical Analysis

The statistical analysis was carried out using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The one-way ANOVA test was used to analyze the potential differences between study groups. In cases where a difference was detected between the groups, the Levene test was used to check the differences between the variances and to identify which group was the source of difference. The variances were not equal when p values were < 0.05 based on the Levene tests, and the Tamhane's and Dunnett's t-test were used in such cases. Variances were considered equal when p values were > 0.05 based on the Levene test, and Scheffe test was used in such circumstances. Based on Scheffe, Tamhane's and Dunnett's t-tests, p values of < 0.05 were considered statistically significant [12]. In this study, a power analysis can be the most suitable measurement for deciding how large a sample size we need for performing the planned experiment? An experiment that is too small may fail to observe biologically important aspects; however, an experiment that is too large may lead to wasting the animals. In order to balance those two sensitive concepts, scientists often asked to justify the number of animals they plan to use. According to power analyses calculation, fourteen rats were decided to be appropriate for each group.

Results

All rats were returned to normal feeding and other activities immediately after the operation, and all rats completed the study and were sacrificed on postoperative Day 12. The mean weight of the rats was 270 (range: 247 to 303) g in the sericin group, 263 (range: 237 to 310) g in the talcum powder group, and 244 (range: 234 to 265) g in the control group meaning no statistically significant difference among the groups.

Results of basic Fibroblastic Growth Factor

The biochemical analysis showed that the mean rat plasma b-FGF levels were 251.7 pg/mL in the sericin group (range: 101 to 821 pg/mL), 72.3 pg/mL in the talcum powder group (range: 24 to 131 pg/mL), and 133.1

pg/mL in the control group (range: 25 to 1320 pg/mL). A significant difference was noted in the Scheffe test results of sericin and talcum powder groups ($p < 0.05$, $p = 0.046$). However, no statistically significant difference between pleurodesis groups and the control group was calculated.

Results of high sensitive C-reactive protein

The biochemical analysis revealed mean rat plasma hs-CRP levels of 1.038 ng/mL in the sericin group (range: 0.677 to 2.815 ng/mL), 1.343 ng/mL in the talcum powder group (range: 0.606 to 5.662 ng/mL), and 0.945 ng/mL in the control group (range: 0.586 to 1.261 ng/mL). A Scheffe test revealed no significant differences among the study groups. The b-FGF and hs-CRP results in the rat plasma are presented in Table 1.

Table 1. Mean values, lower-upper limits and statistical results of rat plasma b-FGF and hs-CRP levels in the sericin, talcum powder and control groups.

Parameters	Sericin (n=14)	Talcum powder (n=14)	Control (n=14)	Statistics (A vs B; p value)
bFGF (pg/mL)	251.7 (range: 101-821)	72.3 (range: 24-131)	133.1 (range: 25-320)	Sericin vs talcum powder ($p < 0.05$, $p = 0.046$)
hs-CRP (ng/mL)	1.038 (range: 0.677-2.815)	1,343 (range: 0.606-5.662)	0.945 (range: 0.586-1.261)	No significant difference between groups

Discussion

Sericin is a natural, macromolecular, and a kind of glue protein that holds fibroin polymers together [3,8]. The predominant amino acid in the structure of the sericin protein is serine amino acid and as such, sericin contains strongly polar side groups, such as hydroxyl, carboxyl, amino groups that enable easy cross-linking, and copolymerization that improves both biocompatibility and biodegradation [13,14]. Sericin has many applications, including as an anti-wrinkle, anti-aging, antioxidant and as an additive to cell culture media, and has a healing effect on wounds [1,2,8,13-16]. Sericin has good hydrophilic properties that are widely used in the pharmaceuticals and cosmetic sectors. Furthermore, it is useful in the wound healing process and can be used as a wound dressing and healing agent [16-18]. Ersel et al. evaluated the in vivo wound healing effects of a gel formulation containing sericin in rats [16]. The epidermal thickness and vascularization of the skin increased, whereas hair root degeneration, edema, cellular infiltration, collagen discoloration, and necrosis decreased more in the sericin group than in the control group [16]. They also noted that levels of antioxidative activity increased in the sericin-treated animals [16]. Based on the findings, the authors concluded that sericin had significant positive effects on wound healing and antioxidant activity [16]. Similar antioxidant activity of sericin has also been described by Yazicioglu et al. [19]. In their study, the authors showed that an intrapleural application of sericin increased plasma native thiol and total thiol levels, which promote antioxidant activity and prevent free radical-induced damage [19].

Pleurodesis refers to the obliteration of the pleural space and the symphysis of pleural layers, preventing the collection of either fluid or air in the pleural space. It is an appropriate approach to use a protein that is already a natural adhesive to glue the pleural surfaces together. The efficacy of pleurodesis and the usefulness of sericin powder was first described by Yazicioglu et al. in a study involving rats [3]. A comparison of the results of sericin pleurodesis with talcum powder, doxycycline, and silver nitrate pleurodesis was described by Yazicioglu et al., in another rat study [4]. Aforementioned these studies demonstrated increased fibroblastic activity and fibrosis induced by sericin pleurodesis [3,4]. These studies also demonstrated the lung parenchyma-preserving activity of sericin powder and reported fewer side effects in the sericin pleurodesis group [3,4]. However, it remains unclear, whether an increase occurred in the levels of several hormones, cytokine and chemokines, as plasma markers of fibroblastic activity. If an increase was noted in fibroblastic activity, these parameters would also be expected to increase.

Talcum powder is the most commonly used agent worldwide in inducing pleurodesis, and is considered to have the highest efficiency [20,21]. In a study by Yazicioglu et al. comparing sericin with other pleurodesis agents, sericin pleurodesis was found to be superior in certain aspects when compared to talcum powder [4]. In

an evaluation of visceral and parietal pleurae based on Masson's trichrome staining, Yazicioglu et al. demonstrated that the collagen fibers in the sericin group were more intense than in the talcum powder group ($p < 0.05$) [4]. Additionally, foreign body reaction and emphysema in the parenchyma were less frequent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. The presence of biological tissue in the parenchyma was less prominent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. Similar to parenchyma, foreign body reaction on the thoracic wall was also less common in the sericin group when compared to the talcum powder group ($p < 0.05$) [4]. Finally, the presence of biological tissue glue on the thoracic wall was less prominent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. In summary, sericin pleurodesis was found to be a superior pleurodesis agent compared to talcum powder. Although pathological outcomes and the success of intrapleural sericin administrations have been demonstrated, there is no data in the literature regarding on its biochemical consequences. Under these circumstances, the effects of intrapleural sericin and talcum powder administration on b-FGF and hs-CRP levels and their comparative efficiencies should be known.

The basic fibroblast growth factor, known also as fibroblast growth factor 2 (FGF2) and FGF-β, is a growth factor and signaling protein encoded by the FGF2 gene [22]. The FGF protein was first purified in 1975, and b-FGF is synthesized primarily as a 155 amino acid polypeptide, resulting in an 18 kDa protein [22,23]. The b-FGF has broad mitogenic and cell survival activities, and is involved in a variety of biological processes, such as embryonic development, cell growth, morphogenesis, and tissue repair [24-26]. The primary source of b-FGF is endothelial cells, its primary target is fibroblasts, and its primary effect is the proliferation of fibroblasts with an extracellular matrix formation [27]. It also stimulates mesothelial cell proliferation both in vivo and in vitro [28]. This factor is mitogenic for fibroblasts, smooth muscle cells, and endothelial cells; and is present in the pleural effusions of tumors [29-31]. Antony et al. reported that the intrapleural instillation of talcum powder induces the pleural mesothelial production of b-FGF, which is responsible for pleural symphysis [31]. Antony et al. identified significantly higher levels of b-FGF in the pleural fluids of patients who underwent successful pleurodesis with talcum powder [31]. Therefore, talcum powder pleurodesis activates pleural mesothelial cells to produce significantly higher amounts of b-FGF when compared to the control group, in malignant pleural effusion patients [31].

It is known that the plasma levels of various growth factors increase after thoracic surgery operations. Dikmen et al. reported that plasma hepatocyte growth factor levels increased significantly at postoperative Days 1 and 3 in patients undergoing lung resection [32]. In the present study, no significant increase was noted in the b-FGF levels of the talcum- and sericin-induced pleurodesis groups when compared to the control group. However, when the sericin and talcum powder groups were compared, the increase noted in the sericin group was statistically significant ($p < 0.05$; $p = 0.046$) (Table 1). The lack of a significant difference between the sericin group and the control group is consistent with the findings of previous studies. In a study by Yazicioglu et al. no significant difference was noted in the b-FGF, TGF- β, and IL-2 levels between the rats undergoing intrapleural sericin administration and the control group [33]. The higher b-FGF levels in the sericin group than in the control group and lower b-FGF levels in the talcum powder group than in the control group suggest that the administration of intrapleural sericin has a stimulatory effect on endothelial cells, mesothelial cells, and fibroblasts. On the other hand, according to Hojski et al., the serum level of b-FGF was higher after mechanical pleurodesis compared to those after chemical pleurodesis [5]. The increased plasma b-FGF levels noted in the rats suggest that sericin can induce an increase in b-FGF levels through its stimulatory effect. Sericin administration increases fibroblastic activity by increasing b-FGF levels, accelerating fibrosis and producing successful pleurodesis. In this study b-FGF level is not significantly high in the talcum powder group compared to the control group. However, Antony et al. demonstrated significantly higher levels of b-FGF in the pleural fluid after talcum powder pleurodesis [31]. This difference may be related to analyzing material was pleural fluid in the study of Antony and colleagues, but the plasma sample in our study.

The C-reactive protein was the first acute-phase protein to be described and is a sensitive systemic marker of inflammation and tissue damage [34]. The acute-phase response comprises most forms of tissue damage, infection, inflammation, and malignancies [34,35]. According to Fang et al., the elevated serum CRP levels

in patients with nasopharyngeal carcinoma are associated with a poor prognosis [36]. Elevated CRP levels are not poor prognostic markers only for malignancies, but plasma CRP levels are also found to increase during infections, and under conditions in which tissue damage has become more extensive and inflammatory response has escalated. In this respect, CRP can be considered an important follow-up parameter.

The CRP gene, located on the short arm of chromosome 1, contains only one intron, and consists of five identical, non-covalently associated protomers that are arranged asymmetrically around a central pole [37]. CRP is produced and synthesized primarily in the liver, in response to inflammatory cytokines, and assists in the phagocytosis of macrophages [35]. It also synthesized in other cell types, such as smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes [38]. CRP is a member of the pentraxin protein group, which is an integral part of the innate immune system [35]. The level of CRP tends to be proportional to the intensity of the inflammatory process, and is sensitive to changes in response to inflammation [35]. Froudarakis et al. examined the systemic inflammatory reaction after thoracoscopic talcum poudrage, and showed that the white blood cell count, percentage of neutrophils, and CRP levels were significantly increased in the group of patients who underwent talcum poudrage [39]. In our study, no significant increase was noted in the CRP levels of the talcum powder group, and this difference in results can be attributed to the fact that Froudarakis et al. studied human subjects, while the present study was conducted on rats. Furthermore, Froudarakis et al. measured CRP levels on day two after surgery, while the rats in the present study were sacrificed on Day 12. Levels of CRP fall quickly due to its short half-life of only 4 - 7 hours [35]. Therefore, hs-CRP levels in the blood are likely to regress and return to normal levels after the alleviation of inflammation.

Although the mean hs-CRP levels in the sericin and talcum powder groups were higher than in the control group, the difference was not statistically significant (Table 1). This finding can be attributed to the short half-life of hs-CRP. In the study by Yazicioglu et al., sericin pleurodesis was compared with pleurodesis induced by talcum powder, doxycycline, and silver nitrate [4]. The authors reported that their study evaluated many parameters, including the inflammatory parameters of the lung parenchyma and chest wall [4]. According to the results of the study conducted by Yazicioglu et al., the evaluation of inflammation in the lung parenchyma indicated that mild, moderate and severe inflammation were noted in three (25%), three (25%) and six rats (50%) in the sericin group, respectively [4]. While there was no inflammation in two rats (18.2%) in the talcum group, moderate and severe inflammation was observed in two (18.2%) and seven rats (63.6%), respectively. The statistical analyses of inflammation in the parenchyma did not reveal any significant difference between the two groups. On the other hand, the evaluation of the inflammation on the thoracic wall indicated that mild, moderate and severe inflammation was noted in two (18.2%), five (45.5%) and four rats (36.3%) in the talcum powder group, respectively. While no inflammatory reaction was detected in three (25%) rats in the sericin group, mild, moderate and severe inflammation was noted in three (25%), three (25%), and three rats (25%) in the sericin group, respectively. Similarly, to the inflammation of the parenchyma, the statistical analyses did not indicate any significant difference between the two groups. As hs-CRP is an inflammation marker, and the lack of any difference in this parameter between the study groups supports the pathological findings of the study by Yazicioglu et al. [4].

There are some limitations to this study. First, we did not evaluate any other fibrosis or inflammation markers, such as transforming growth factor-β1, vascular endothelial growth factor, platelet derived growth factor, interleukin-2,-8,-10 and various other cytokines. Other markers of fibrosis were not evaluated, as it was not clear whether an increased fibroblastic activity would increase the plasma levels of b-FGF. This pilot study identified an increase in b-FGF levels, and investigations of other cytokines and chemokines in subsequent studies would further facilitate our understanding of fibrosis mechanisms.

In conclusion, sericin is a natural intrinsic protein, and sericin pleurodesis is a successful, better-tolerated, more cost-effective, and investigable approach with low potential for side effects. Increased fibroblastic activity in response to sericin pleurodesis has not been demonstrated biochemically, to date. The findings of significantly higher b-FGF levels in the sericin pleurodesis group than in the talcum powder pleurodesis group indicates a higher efficiency of sericin in the induction

of pleurodesis. Based on these results, the success of intrapleural sericin administration in inducing pleurodesis can be biochemically confirmed. On the other hand, hs-CRP, a marker of inflammation, was not found to be significant, and it is considered that hs-CRP returned to normal levels due to its short half-life. The researches of sericin as a pleurodesis agent will add value to the practice of thoracic surgery and pulmonology.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

Acknowledgement: The authors have special thanks to Prof. Dr. Yahsi Yazicioglu from Gazi University for statistical analyses.

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To cite this article: Erdoğu V, Metin M, Sayar A, Büyükkale S, Kılıçgün A, Kanbur Metin S Pekçolaklar A, Çıtak N, Ürer HN, Gürses A. Does frozen section increase false negativity in cervical mediastinoscopy during mediastinal lymph node staging compared to paraffin section? Curr Thorac Surg 2020; 5(1): 31-35.

Original Article

Does frozen section increase false negativity in cervical mediastinoscopy during mediastinal lymph node staging compared to paraffin section?

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ABSTRACT

Background: Cervical Mediastinoscopy (CM) is the most important invasive method in mediastinal lymph node staging. Lymph nodes dissected via CM can either be sent to frozen section (FS) for analysis allowing thoracotomy to be performed on the same session, or to paraffin section (PS) where thoracotomy is performed as a separate session (as a separate operation). This study compares the false-negative ratio of mediastinoscopic FS and PS analysis.

Materials and Methods: 454 patients with primary lung cancer who have undergone CM between January 2003 and December 2005 have been retrospectively analysed. This study evaluates whether FS analysis increases the false-negative rate of lymph node biopsies.

Results: 160 cases from the PS group and 113 cases from the FS group were included in the study. The mean age of the patients was 56.4 years (range 28-77 years). There were 260 men and 13 women. In the PS group, mean thoracotomy time after CM was 9.9 days. False negativity of CM in the PS and the FS groups was found to be 9.2% and 8%, respectively.

Conclusion: There was no statistically significant difference in terms of false negativity between FS and PS in mediastinal staging ($p = 0.598$).

Keywords: Frozen section, paraffin section, lung cancer staging

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Doi: 10.26663/cts.2020.0005
Received 04.09.2019 accepted 06.11.2019

Introduction

The most important criteria in determining treatment modality and disease prognosis in lung cancer without distant metastasis is, the state of the mediastinal lymph nodes [1-2]. Cervical mediastinoscopy (CM) accepted as the gold standard method for invasive mediastinal staging. CM has 78% specificity, 100% sensitivity and 91% negative predictive value (NPV) in mediastinal staging [3]. The biggest disadvantage of CM is, the procedure's false negativity rate. In previous studies this rate has been found to be 1-10% [4]. Non-surgical treatment is the primary modality for patients determined to have positive mediastinal lymph nodes (pN2) using CM [5,6]. Appropriate mediastinal staging reduces the number of patients undergoing unnecessary thoracotomy. Indications for CM are defined as; lymph node greater than 1 cm on computed tomography (CT), positive mediastinal and/or hilar lymph node on Positron Emission Tomography-Computed Tomography (PET-CT), central or large peripheral tumor and a histology of adenocarcinoma [7].

The aim of this study is to evaluate whether there is a significant difference between the false- negativity rates of frozen section (FS) and paraffin section (PS) methods in CM lymph node staging in patients diagnosed with primary lung cancer without distant metastasis.

Materials and Methods

454 patients diagnosed with primary lung cancer undergone CM or thoracotomy on the same or different sessions were retrospectively recorded between January 2003 - December 2005 in Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital. All of the patients were diagnosed and clinically staged with radiological and broncological procedures. Patients without mediastinal lymph node metastasis (pN0), were surgically treated with a lobectomy on the same session or at least on one of the next sessions. The sampled lymph nodes were staged with The American Joint Committee on Cancer (AJCC) staging system revised in 2009, as recommended by Mauntain [8]. The decision whether thoracotomy should be made on the same session or a different session was made by the surgeons. All of the patients who were treated in our clinic gave informed consent by signing a statement allowing the use of their data for clinical trials. The study was approved by the local institutional review board (2020-240-01) and was conducted in accordance with the principles of the Declaration of Helsinki.

In FS group, lymph nodes were sent to the pathology laboratory without fixation. Lymph nodes were analysed by both imprinting and by freezing methods making 1 or 2 slices. Frozen section results were reported after an average of 25 minutes. In PS group, the lymph nodes sent by fixed in formaldehyde then added to paraffin blocks by pathologists and were analysed after being dissected into at least 3 slices. Both FS group and PS group, the specimens were evaluated by 3 pathologists who were specialized in lung cancer in our clinic. Immunohistochemical staining was not used in any of the patients. The patients that were found to be pN0 on the FS analysis were treated with thoracotomy on the same session, while patients who were found to be pN0 with PS were treated with thoracotomy after a mean of 9.9 days. The patients diagnosed as pN2 and/or pN3 in the opposite mediastinum were referred to oncology departments for adjuvant or neoadjuvant therapy. European Society of Thoracic Surgeons (ESTS) guideline published in 2004 was taken as reference in intraoperative mediastinal staging methods due to the differing preferences of the surgeons whether to perform systemic mediastinal lymph node dissection or a biopsy of lymph nodes solely in thoracotomy. Hence, it was obligatory to sample at least 3 mediastinal lymph nodes with one being the subcarinal (number 7) station in the lobe's drainage pathway [9]. The standard cervical mediastinoscopy method was used in the study. Video-assisted mediastinoscopic lymphadenectomy (VAMLA) or videomediastinscopy methods were not used during the study time in those years.

55 patients (12 PS, 43 FS) were excluded from the study because they couldn't be intraoperatively staged so their false negativity in CM couldn't be analysed. 59 patients were excluded from the study for receiving neoadjuvant therapy. 24 patients although reported as pN0 in CM, were either operated on in another clinic or refused surgical treatment, 33 cases who could only be surgically explored during thoracotomy due to tumor size and local invasion, were excluded from the study. 9 cases were excluded from the study due to complications (haemorrhage, severe arrhythmia, etc.) that occurred during CM causing insufficient mediastinal lymph node sampling and 1 case was excluded from

the study because of peroperative exitus. According to these criteria, a total of 181 patients were excluded from the study, and a total of 273 patients, of whom 160 were from the PS group and 113 were from the FS group were included in the study.

Statistical Analysis

The data were entered in the Statistical Package for the Social Sciences (SPSS 23.0 version for Windows; SPSS Inc., Chicago, Illinois, United States). Age; gender; pN status; has been analyzed. Student-t test was used in comparison of false negativity, sensitivity, specificity and negative predictive value results values between groups. Pearson's chi-square test was used for the analysis of qualitative variations. $p < 0.05$ value was considered statistically significant.

Results

The mean age of the patients included in the study was 56.4 years (range 28-77 years). There were 260 men and 13 women. In the PS group, mean thoracotomy time after CM was 9.9 days. The CM sampling was reported as pN0 in 120 of 160 patients (75%) and 40 patients (25%) were reported as pN2-3. These patients were referred to the oncology department for adjuvant or neoadjuvant treatment. Among the patients who have undergone thoracotomy, 27 patients (22.5%) who could not be diagnosed with invasive or non-invasive techniques prior to thoracotomy, were diagnosed as pN2 even though they were not expected to have single or multiple station positivity. Out of these 27 pN2 patients, 11 (6.8%) were missed due to false negativity of CM, even though their lymph node stations could be easily accessed (2R-2L-4R-7). The sensitivity, specificity, NPV and false negativity ratio of CM procedure with PS was recorded as 82.2%, 100%, 90.8%, and 9.2% respectively (Table 1).

Table 1. FS and PS group false negativity, sensitivity and specificity, negative predictive value results.

Method	Number of patients	CM pN0	CM pN2-N3	Thoracotomy pN2 (4R-7) False %	Sensitivity %	Specificity %	NPV %
FS	113	75	38	8	88	100	92
PS	160	120	40	9.2	82.2	100	90.8
P value			0.120	0.598			

Abbrev.; FS: frozen section, PS: paraffin section, NPV: negative predictive, CM: cervical mediastinoscopy

75 of the 113 patients (64.4%) in the FS group were found to be pN0. 38 (33.6%) patients were reported as pN2-3 in CM and these patients were referred to Oncology Department for adjuvant or neoadjuvant treatment. Among all the patients who have undergone thoracotomy, 18 (24%) who could not be diagnosed via invasive or non-invasive techniques prior to thoracotomy, were diagnosed as pN2. 6 of the 18 patients (5.3%) were missed because of the false negativity of CM, although the lymph node stations were accessible with CM (2R-2L-4R-4L-7). The sensitivity, specificity, NPV and false negativity ratio of CM procedure with FS was recorded as 88%, 100%, 92%, and 8% respectively (Table 1).

Among patients who have undergone thoracotomy and diagnosed as pN2 in lymph node station number 7, 4 patients (4/6- 33%) were from the FS group and 9 patients (9/11- 81.8%) from the PS group. In both groups, 2 patients were found to be 4R false negative (2/6- 33% in the FS group, 2/11- 18% in the PS group) (Table 2).

Table 2. PS and FS false negativity in lymph node stations.

Lymph node station	pN2 diagnosed in thoracotomy following PS (Number of Patients)	pN2 diagnosed in thoracotomy following FS (Number of Patients)	p
4R	2	2	> 0.05
7	9	4	> 0.05
4R+7	11	6	> 0.05

Abbrev.; 4R: right lower paratracheal lymph node, 7: subcarinal lymph node, FS: frozen section, PS: paraffin section

Discussion

Mediastinal lymph node involving is the most important factor in defining the prognosis in lung cancer. 15-26% of the patients are found to be pN2 during thoracotomy in patients initially diagnosed as pN0 with invasive and non-invasive techniques. This group has the best survival rate among the pN2's. The treatment suggested to these patients is achieving the negative surgical margin (R0) followed by adjuvant therapy. 5 year survival rate is around 30% [10]. In our study, although not expected in thoracotomy, we found pN2 in 22-24% of the cases, which is similar to the results in published literature.

In literature, false negativity in CM is between 1-10%. The highest false negativity is found in subcarinal lymph nodes, and less frequently in the 4R station. Lamaire et al. have recorded a diagnosis of pN2 during mediastinoscopy as 23%, and the false negativity ratio as 5.5% [11]. The false negativity ratio between PS and FS in our study was recorded less than 10% as in literature, and there was no statistically significant difference. Most frequent false negativity in both groups was seen in subcarinal lymph nodes.

The advantages of FS analysis include patients undergoing anesthesia only once, same session thoracotomy option and one time hospitalization which causes cost reduction. In a study where patients' opinions were taken, the result was that patients want to undergo CM thoracotomy on the same session. The disadvantage of FS analysis is, since it is a peroperative procedure, one slice is excised unless more is needed, and this could be a problem in identifying metastasis. Also, dysmorphology may occur due to the freezing of the piece. However, studies have shown that this is not a disadvantage. Moreover, the slice excised for analysis, even if only imprinting method is used, has found to be advantageous to that of FS because it saves time and there is more sample area to be analysed and also their false negativity ratio is similar. On the other hand in paraffin section analysis is made through three slices, unless more is needed, which is advantageous in identifying metastasis. However, studies have shown that there is no significant difference compared to FS analysis [12].

Our study had a few limitations of note. First, this was a single-center study based on a relatively small number of patients. Second, the patients underwent operations performed by several surgeons. Third, videomediastinoscopy wasn't used. Fourth, pathological examinations performed several pathologists. Fifth, our conclusions are based on a retrospective analysis of patient data. Accordingly, further researches into prospective designed studies are suggested.

In conclusion, mediastinal staging is one of the most important prognostic factors in non-small cell lung cancer patients. Mediastinal staging also provides a therapeutic strategy for patients. The cervical mediastinoscopy is still considered the gold standard in mediastinal staging. In this study, we investigated whether the FS method increases the false negativity of cervical mediastinoscopy compared to the PS method. We could not find any difference between the two groups. FS is a safe method for evaluating CM results.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

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To cite this article: Doğru MV, Kilimci U,Sezen CB, Dinçer Sİ, Ürer HN. Thoracoscopic resection of a mediastinal lymphangioma: a rare case. Curr Thorac Surg 2020;5(1):36-39.

Case Report

Thoracoscopic resection of a mediastinal lymphangioma: a rare case

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ABSTRACT

Lymphangiomas are often congenital benign tumors that are formed by abnormal proliferation and development of lymphatic tissues. Although it may be localized in all lymphatic chain regions, intrathoracic localization has been reported rarely. Here we present a case of a 24-year-old non-smoker male patient admitted to our clinic with an incidentally found well-circumscribed radioopacity located in the right upper zone of the mediastinal region detected on routine chest x-ray. The computerized thorax tomography revealed a thin layered, fine-lined lesion with cystic content of 8x6 cm, located at the right paratracheal level. The patient underwent a video-assisted thoracoscopic excision of the cyst, and lymphangioma was confirmed based on the histopathologic examination. Although various alternative treatment methods such as chemotherapy, radiotherapy, sclerosing therapy, and laser therapy are used in the treatment of lymphangioma However, their effects on the treatment vary widely in the reported publications.

Keywords: cystic lymphangioma, mediastinum, video-assisted thoracoscopic surgery, minimally invasive surgery

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Doi: 10.26663/cts.2020.0006
Received 13.08.2019 accepted 14.11.2019

Introduction

Lymphangiomas are often congenital, benign tumors that are formed by abnormal proliferation and development of lymphatic tissues. Three pathological types defined were; simple, cavernous and cystic forms. Cystic lymphangiomas are surrounded by a fibrous pseudocapsule that are large and commonly multiloculated. Although they might be localized in all lymphatic chain regions, intrathoracic localization has been reported rarely and the superior mediastinum is the site that the lesion resides in the intrathoracic region. It may cause symptoms such as cough, dyspnea, stridor, dysphagia and hemoptysis due to compression of the neighboring structures such as superior vena cava, trachea, ductus thoracic, esophagus, left and right brachiocephalic vein. Thereto patients might present with vena cava superior syndrome, chylothorax, Horner's syndrome, constrictive pericarditis, and secondary infections. Mostly they are diagnosed at the first two years of age, however, because of their slow growth and deep settlements, they can be detected in adulthood, either incidentally or when became symptomatic [1].

We here present an incidentally diagnosed giant cystic lymphangioma, which was located in the right paratracheal area and excised via video-assisted thoracoscopic surgery (VATS).

Case Report

A 24-year-old non-smoker male patient admitted to our clinic with an incidentally found well-circumscribed radioopacity located in the right upper zone of the mediastinum during a pre-marital routine chest x-ray examination. Computerized thorax tomography (CT) revealed a thin-layered, fine-lined 8x6 cm cystic lesion located at the right paratracheal level (Figure 1).

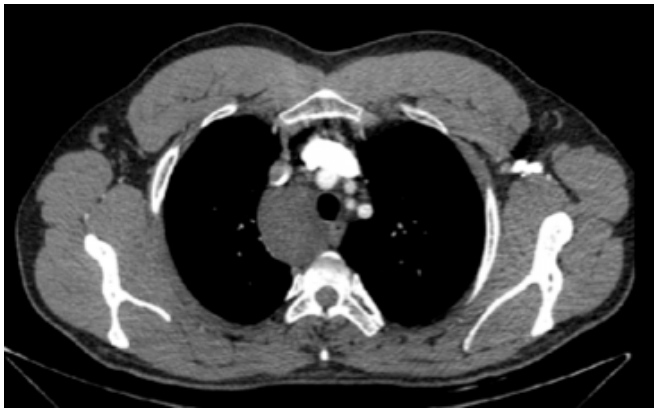

Figure 1. Thorax CT showing a thin layered, fine-lined lesion with cystic at the right paratracheal level.

The physical examination was normal. He described a decrease in his exercise capacity during the last 3 years, without causing a problem to his daily routines. There were no abnormalities in the routine blood tests, EKG and pulmonary function test (FEV1: 4.61 L, %105.8, FVC: 4.62, %89.8)

Surgery was planned with the initial diagnosis of a bronchogenic cyst and considering the deep mediastinal localization, vascular surroundings and the abundance of cystic nature, no preoperative invasive diagnostic procedure was done.

The exploration was done via two-port VATS, under general anesthesia with double-lumen endotracheal tube intubation. An uninoculated cystic mass, which was located in the right paratracheal area, in close relation to vena cava superior anteriorly, vena azygos inferiorly, transverse process posteriorly and extending up to second rib level superiorly was observed (Figure 2). After excision of the mediastinal pleura, the deep extension of the cyst between vena azygos, vena cava superior, and the brachiocephalic vein was seen. The cyst was aspirated which was clear and straw-like colored, to reach the root for complete dissection to prevent injury to vessels. After the root of the lesion was released from the posterior side of superior vena cava, it was separated from the mediastinal fatty tissue by using an endolinear stapler. After inserting one apicobasal chest tube, the operation was terminated without any complication.

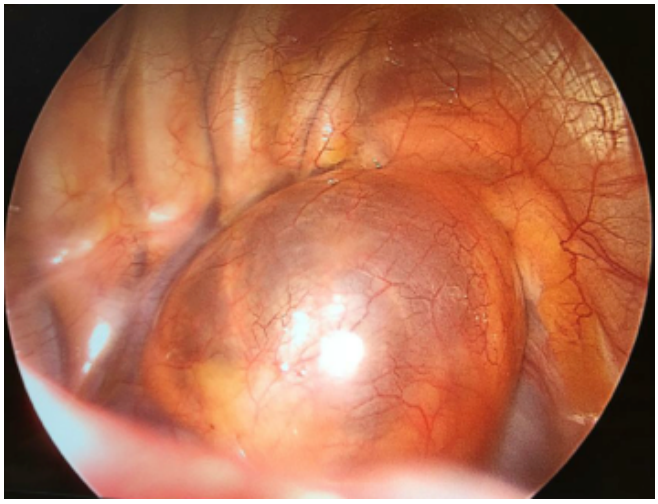

Figure 2. Intraoperative view showing the lesion that was located at the right paratracheal area, near vena cava superior anteriorly, vena azygos inferiorly, transverse process posteriorly and extends up to the second rib superiorly.

The patient was uneventfully discharged on post-operative day 3. In the histopathological examination of the lesion, CD31 and D2-40 antibodies were stained positive which was compatible with cystic lymphangioma (Figure 3).

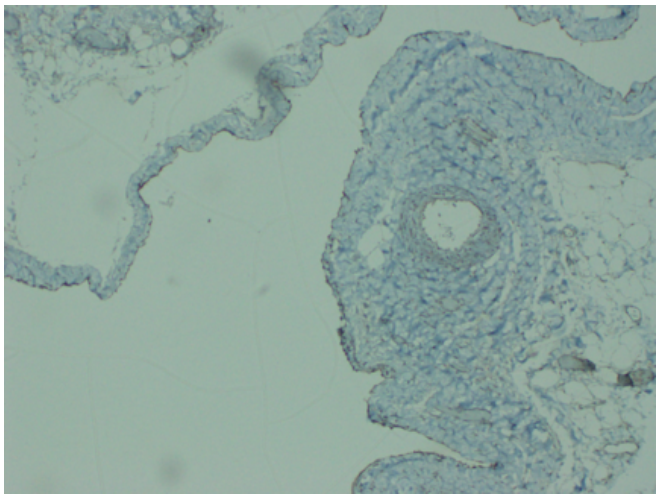

Figure 3. The lesion stained immunohistochemically with D2-40 (x200).

Physical examination was normal at three month follow-ups, and CT scan revealed no recurrences at the first-year control.

Discussion

Lymphangiomas often described as congenital malformations that are accused by lymphoid tissue insufficiency, lymphoid-venous junction problems, gemmation abnormalities, and/or sequestration of embryonic lymphoid tissue [2]. These lesions are typically thin-walled and mostly multilocular but may also be unilocular, as in our case. The content may be serous or chylous fluid [2,3]. Although mediastinal cystic lymphangiomas are rare, some cases exist in the literature [4-12]. Cystic lymphangioma was diagnosed in only 5 (1.8%) of 279 patients who underwent excision for the mediastinal cyst [6].

Mediastinal cystic lymphangiomas are rarely seen lesions that are typically located in the superior mediastinum and at the right hemithorax. Bronchogenic cysts, thymic cysts or thymomas, coelomic cysts, enteric cysts, and ductus thoracicus cysts should be considered at the differential diagnosis. Most of the lymphangiomas detected in adulthood are asymptomatic. However, patients can be presented with symptoms such as chest pain, cough, dyspnea, stridor, dysphagia due to compression of intrathoracic structures. Hoarseness due to vocal cord paralysis and swelling of the neck due to venous compression may be observed.

The recommended radiological imaging methods for the diagnosis of the cystic lesion are x-ray and thorax CT. In our case, the chest x-ray showed a mediastinal widening and the thorax CT imaging revealed a cystic, well-circumscribed and homogenous soft tissue lesion. Three-dimensional ultrasound imaging is also useful for detecting fine septations compatible with lymphangioma. MRI scanning helps to accurately predict relations between the lymphatic chain and other mediastinal organs [1]. Cystic lymphangiomas characteristically immunohistochemically stained positive with CD31 and D2-40 [13].

The standard treatment modality is complete surgical excision via thoracotomy or VATS, as performed in our case. Surgical resection is necessary both to confirm the diagnosis and to prevent complications that may occur due to the compression effect on vital organs. Surgical removal of the cyst wall should be achieved completely. The success of totally excised cases is quite high. As we have performed, cysts in larger sizes can be completely resected after aspirating its content, to reveal the borders in the full sense and not to injure vascular structures.

Some authors predicted that cystic lesions might be in communication with the ductus thoracicus. Thus, in the preoperative period, the administration of olive oil from a nasogastric catheter was suggested. However, we did not prefer this method in this particular case [2].

Some authors suggest that these cysts can be excised by enucleation. Whichever the method is, it should be kept in mind that, there is a risk of recurrence in incomplete resections. We have not found any sign of recurrence after a one-year follow-up in our patient. Esme et al. reported significantly lower morbidity, mortality, and recurrence rate in patients undergoing surgery for mediastinal cysts, compared to conservative approaches [14]. Nowadays, surgical excision with VATS is used safely for curative treatment of many mediastinal cystic lesions in experienced centers. In the study of Ulaş et al. [15], VATS and conventional thoracotomy methods were compared in the surgical approach to mediastinal cysts, and it was statistically significant that the patients of the VATS group had lower hospitalization length and operation duration. Moreover, VATS patients had no increase in the means of intraoperative bleeding, postoperative complications, and incomplete resection risk. In

that vein, we did not encounter any kind of intraoperative or postoperative complications, and the patient was discharged from the hospital three days after surgery with complete recovery. In our center, the first choice for the approach to mediastinal cystic lesions has been excisional intervention with VATS.

In conclusion, the surgical approach is the curative treatment method for mediastinal cystic lymphangioma cases, and nowadays, the VATS procedure should be preferred primarily as it significantly reduces the operation time and postoperative hospital stay.

Declaration of conflicting interests

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

Funding

The authors received no financial support.

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Current Thoracic Surgery

To cite this article: Yazgan S, Gürsoy S, Üçvet A, Acar A, Samancılar Ö, Özer F. What you don't want to see after a superior sulcus tumor resection?: a tension pneumocephalus. Curr Thorac Surg 2020;5(1):40-42.

Case Report

What you don't want to see after a superior sulcus tumor resection?: a tension pneumocephalus

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ABSTRACT

A case of tension pneumocephalus following a superior sulcus tumor resection is presented. The symptoms, diagnostic methods, and treatment options are discussed and reviewed.

Keywords: pneumocephalus, complication, superior sulcus tumor

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Doi: 10.26663/cts.2020.0007
Received 14.11.2019 accepted 12.12.2019

Introduction

Pneumocephalus is a rare condition that defines the pathologic presence of the intracranial air. It is often seen after trauma (skull base or sinus fractures), neoplasms, infections and intracranial operations. Pneumocephalus, which occurs after thoracic operations is rare, but a possible mortal complication. D'Addario reported the first case of pneumocephalus developed after a thoracic operation in the literature in 1974 [1]. Since then, the pneumocephalus after thoracic surgical operations in the literature is rare.

Here we present a case of pneumocephalus, as a complication of a non-small cell superior sulcus lung tumor resection.

Case Report

A 70-year-old male patient referred to our hospital with a complaint of cough. The routine examinations and laboratory tests were done and a mass in the right upper lobe of the lung was detected on thorax CT. Transthoracic needle aspiration biopsy was performed, and squamous cell lung cancer was diagnosed. No distant metastasis was detected in PET/CT scan. The patient, whose tumor was considered as a superior sulcus tumor, received two cycles of neoadjuvant chemotherapy (carboplatin and paclitaxol), and a partial response was obtained. The thoracic magnetic resonance imaging (MRI) of the patient revealed no findings of tumor invasion to any vascular or neural structures. The patient underwent a right upper lobectomy and resection of the first three ribs via a Shaw-Paulson incision. There were no complications in the early postoperative period. On the fifth postoperative day, he developed impaired consciousness and his head deviated to the left side as shown at the chest x-ray (Figure 1).

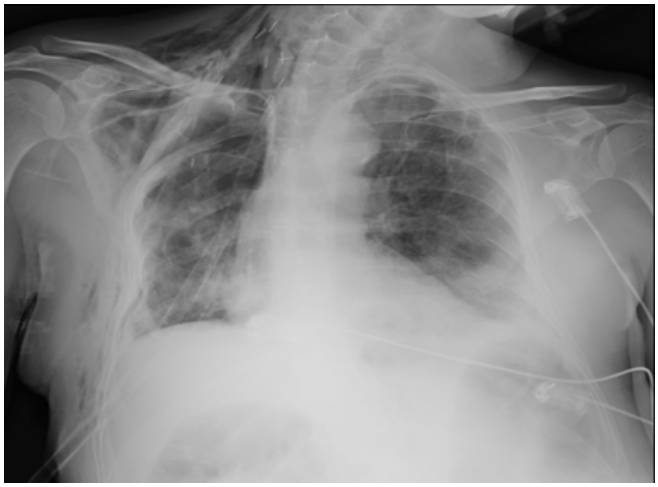

Figure 1. Chest x-ray on postoperative day 5.

Pneumocephalus and shifting to the left of the midline was detected in the brain computed tomography (CT) scan (Figure 2a).

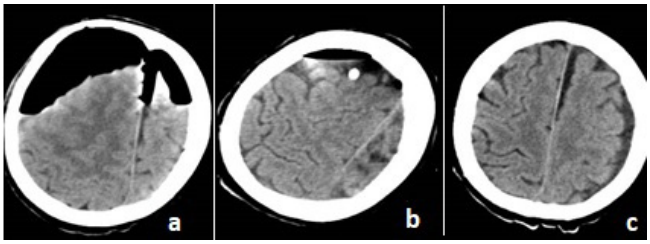

Figure 2. Brain CT scans; **(a)** initial pneumocephalus on postoperative day 5, **(b,c)** control.

Air decompression was performed via single burr hole drainage by neurosurgeons. Post-procedure Glasgow coma scale of the patient increased from 5 to 12 within 48 hours. The patient was followed up in the Trendelenburg position for a period after the cranial operation. Broad spectrum antibiotics were given to prevent meningitis and encephalitis. There was a regression in pneumocephalus in the control brain CT scan (Figures 2b,c), and the cranial drain of the patient was removed on the postoperative day 8 after an improvement in the neurological condition was observed. Chest drains were removed after the air drainage stopped. However, due to pulmonary infection and respiratory insufficiency, the patient was intubated, and the follow up in the intensive care unit continued with mechanical ventilation support. Despite antibiotic administration and mechanical ventilation, unfortunately the patient died due to severe pulmonary infection and hypoxia on day 12.

Discussion

Pneumocephalus after superior sulcus operations is thought to occur due to extensive dissection around the intercostal nerve root, or due to a dural tear caused by excessive rib retraction resulting from stretching of the intercostal nerve. As for in the postoperative period of the patients whose chest drains were removed, a positive intrapleural pressure resulting from an air leak from the pulmonary parenchyma may form pneumocephalus through this dural tear.

In the literature, the number of days between the operation and the onset of pneumocephalus findings varies considerably. Pneumocephalus may present in the early postoperative period, as well as in the relatively later period, such as the 19th day or 30th day [2,3]. This difference also depends on the differences or severity of the pathophysiology of the pneumocephalus mentioned

above. The pathogenesis in our patient was thought to be a dural injury that may have occurred during the tumor dissection. Our case was presented on the fifth postoperative day, and the Glasgow coma scale was 5.

When the symptoms of pneumocephalus are examined, the headache is always present. Deterioration in the mental status, loss of consciousness, nausea, vomiting, vertigo, aphasia, dysphasia, hemiplegia are common, but, these are nonspecific findings for the pneumocephalus. The most specific finding for the pneumocephalus is the splashing sound (bruit hydro-aerique) heard by the patient as a result of moving the patient's head quickly [4]. The initial pneumocephalus symptoms of our patient were impaired consciousness and deviation of the head to the left side. The deviation of the head may occur in several cranial pathologies. But since there is no report in the literature about its relationship with postoperative pneumocephalus cases, we believe the awareness of this symptom could help to diagnose the patient earlier.

In the treatment of the pneumocephalus seen after the thoracic surgery operations, there is not yet a consensus on the literature. Conservative treatments such as bed rest, upside-down position (Trendelenburg position), antibiotic prophylaxis, re-chest tube drainage are discussed to be sufficient for some patients [5]. When a subarachnoid-pleural fistula is diagnosed during the thoracotomy, the fistula should be repaired with a suture ligation or a vascularized muscle pedicle. Also, surgical tissue adhesives can be used to seal the fistulae [5]. If tension pneumocephalus is present, cranial decompression also takes part in the treatments [6]. When the conservative treatments are unsuccessful, there are also publications recommending re-operations to repair the dural tear that occurred [7].

Pneumocephalus is a severe and mortal complication. Especially in patients with superior sulcus tumors, it may be seen even in non-operated patients [8]. For this reason, clinical awareness is essential. It should not be forgotten that pneumocephalus can be seen not only in the superior sulcus tumor surgeries but also after the epidural anesthesia practices [9].

In conclusion, it should be kept in mind that pneumocephalus may develop in the superior sulcus tumor resection for the early recognition of this rare complication. When pneumocephalus is detected, a rapid solution should be produced, and a treatment plan must be made with the neurosurgery department. If a shift is present, cranial decompression should be performed, and the conservative and/or surgical treatment should be planned promptly depending on the etiology with a multidisciplinary approach.

Declaration of conflicting interests

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

Funding

The authors received no financial support.

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To cite this article: Çelik EÇ, Yağcı T, Üçvet A, Gürsoy S, Aydoğdu Z. A rare case: Castleman's Disease. Curr Thorac Surg 2020;5(1):43-45.

Case Report

A rare case: Castleman's disease

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ABSTRACT

Castleman's disease is angiofollicular lymph node hyperplasia that occurs as a result of abnormal proliferation of plasma cells and B lymphocytes in lymphoid tissues. It has been shown to be associated with HHV-8 and HIV infections and may be unicentric or multicentric. This case is presented due to its rareness, good prognosis after complete surgery for unicentric type, and dramatically improved symptoms.

Keywords: Castleman's disease, mediastinal mass, HHV-8/HIV

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Doi: 10.26663/cts.2020.0008
Received 25.12.2019 accepted 10.02.2020

Introduction

Castleman's disease is a rare, non-clonal, lymphoproliferative disorder of unknown etiology, first described by Benjamin Castleman in 1954 [1-3]. It is categorized into two clinical subtypes as unicentric (localized) and multicentric [4]. Variable clinical findings may be observed. Thorax is affected in 70% of the cases. It has been shown to be associated with human herpes virus 8 (HHV-8) and human immunodeficiency virus (HIV) infections [4-6]. Unicentric type has been reported to have a good prognosis following complete resection [7]. This case is presented due to the rarity of intrathoracic unicentric Castleman's disease diagnosed through surgery.

Case Report

A 46-year-old female patient presented with cough, dyspnea, and dysphagia. Physical examination was normal. Chest x-ray revealed an enlarged mediastinum. Computed tomography of the thorax showed an 8x5x11 cm mass lesion located in the subcarinal area, pushing the distal part of the right main bronchus and trachea forward and causing external compression of the esophagus lumen (Figure 1).

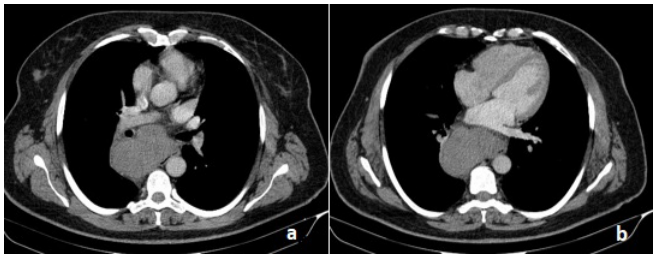

Figure 1. Thorax CT showing the mass lesion, **(a)** pushing the distal part of the right main bronchus, **(b)** causing an external compression to the esophagus lumen.

The right posterolateral thoracotomy incision revealed a mass lesion of approximately 14 cm located in the posterior mediastinum extending into the subcarinal area and azygos vein. The lesion was resected with the capsule. Invasion into the surrounding tissues was not observed. Final pathology was reported as Castleman's disease (Figure 2). All symptoms of the patient, particularly dysphagia, regressed. The patient is still being followed up uneventfully in the 26th month.

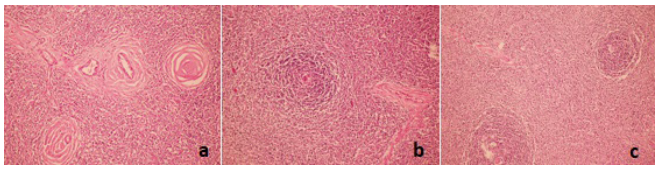

Figure 2. Histopathologic examination showing, **(a)** onion skin appearance, **(b)** perivascular hyalinization, **(c)** vascular proliferation (HEx200).

Discussion

Castleman's disease, also known as angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disease [8]. It was first described by Benjamin Castleman in a patient with localized mediastinal mass in 1954 [1]. The generalized type of the disease was described by Gaba et. al in 1978 [9]. The disease can arise anywhere lymphoid tissue is present, as well as in the thoracic cavity especially in mediastinum and hilum. It is thought that various infectious agents (EBV, human herpes virus-8), inflammatory reactions (interleukin-6, vascular endothelial growth factor) and hamartomatous development play a role in the etiology [10-12].

It has two types as multicentric and unicentric [3,7]. Unicentric type is often asymptomatic, more common in women than in men, and no etiological factor has been identified [4,8,13]. It is seen in the 3rd or 4th decade of life and malignancy potential is low. It is mostly located in mediastinal lymph nodes. It may also be observed in the neck, axilla, retroperitoneal region, mesentery and pelvis [14]. Surgical treatment is curative and the symptoms regress after surgery [15,16]. Five-year survival has been reported to be 100% [2]. Our case was also diagnosed in the fourth decade, being consistent with the literature, and her symptoms improved after surgery. No etiological factor was identified. The lymph node was completely resected with the capsule and there was no invasion outwards.

Multicentric type is more common than unicentric and it is associated with HIV and HHV-8 more frequently [4,8,17]. Fever, night sweats, weakness and massive lymphadenopathy are the most common symptoms [18]. Surgical excision is the best method for diagnosis. However, it is not always possible to excise due to invasion into the surrounding tissue and hypervascularization. Systemic chemotherapy, antiretroviral agents,

interferon alpha, immunomodulatory drugs, rituximab and corticosteroids are recommended for treatment [4]. Multicentric type has a worse prognosis than unicentric type [7]. Patients should be followed closely.

In conclusion, Castleman's disease is a rare lymphoproliferative disease. It is mostly located in the mediastinum. Surgical excision is curative for localized type, dramatically improving the symptoms and the prognosis is excellent.

Declaration of conflicting interests

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

Funding

The authors received no financial support.

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Current Thoracic Surgery

To cite this article: Ürek Ş, Yalçınkaya İ, Gördebil A. A rare case of giant thymolipoma. Curr Thorac Surg 2020;5(1):46-49.

Case Report

A rare case of giant thymolipoma

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ABSTRACT

Thymolipoma is one of the benign pathologies of the mediastinum that may reach large sizes over time and even become a giant mass that fills the hemithorax. It may cause respiratory distress and even failure, and may be accompanied by myasthenia gravis or other clinical conditions. Surgical excision of the mass provides both diagnosis and treatment.

Keywords: mediastinum, thymolipoma, surgery

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Doi: 10.26663/cts.2020.0009
Received 24.12.2019 accepted 27.01.2020

Introduction

Thymolipoma is one of the rare benign neoplasms of endodermal and mesodermal origin, which contain mediastinal fat tissue and thymic elements in different proportions. The term thymolipoma was first defined in the literature by Hall in 1949 [1]. Since then, it has also been called lipothymoma, thymic tissue residue mediastinal lipoma, benign thymoma and lipomatous hamartoma.

Thymolipoma is generally asymptomatic [2,3]. However, when the thymolipoma reaches a large size, it may cause respiratory distress and even respiratory failure. It may also be associated with clinical conditions such as myasthenia gravis and aplastic anemia [1,4,5]. It is difficult to differentiate small thymolipomas from other anterior mediastinal masses on chest x-ray. Large-sized lesions of thymolipoma may mimic cardiomegaly by erasing the contours of the heart [1].

Thymolipoma has been reported in the literature as single case presentations or small case series. Therefore, we aimed to present this case due to its rarity, discussing the diagnosis and treatment with the help of relevant literature.

Case Report

A 52-year-old male patient was admitted to our clinic with bloody sputum and dyspnea. The patient was diagnosed with chronic obstructive pulmonary disease (COPD) three years ago and medical treatment was started. At patient's first admission to our hospital, he was first evaluated by chest x-ray and Morgagni hernia was considered as a preliminary diagnosis (Figure 1).

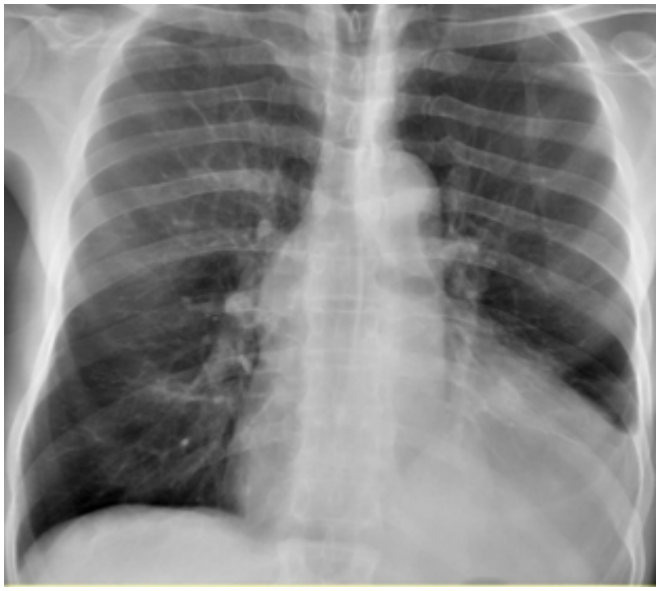

Figure 1. Chest x-ray at the first admission.

Unfortunately, the patient refused furter examination and treatment. At the second admission nine months later, he had only dyspnea. The patient was reevaluated by chest x-ray and thorax computed tomography (CT) scan. Thorax CT scan revealed a 16x12.5x8.5 cm lesion containing largely fat-density and prominent vascular structures in the middle lower mediastinum (Figure 2).

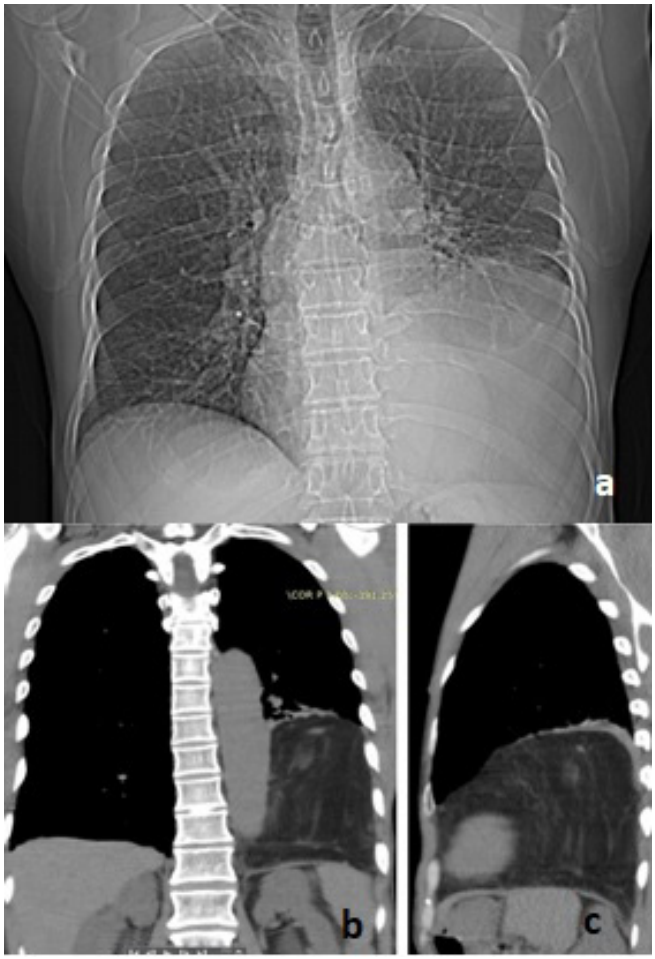

Figure 2. Chest x-ray **(a)**, thorax CT showing the lesion of fat density **(b,c)**.

Lipoma was suspected as the radiological preliminary diagnosis. The forced exhalation volume in one second (FEV1) value was 1.90 L (57%) and the FEV1/ forced vital capacity (FVC) was 78%. The differential diagnosis included lipoma and diaphragmatic eventration.

VATS was planned for exploration. The patient was intubated with double-lumen endotracheal tube and placed in the lateral decubitus position. The diaphragm was intact during exploration, and an extrapulmonary lipomatous mass associated with mediastinum was detected on the diaphragm. The operation was converted from video-assisted thoracoscopic surgery (VATS) to open thoracotomy because of the large size of the lesion. The mass was totally excised via left thoracotomy (Figure 3).

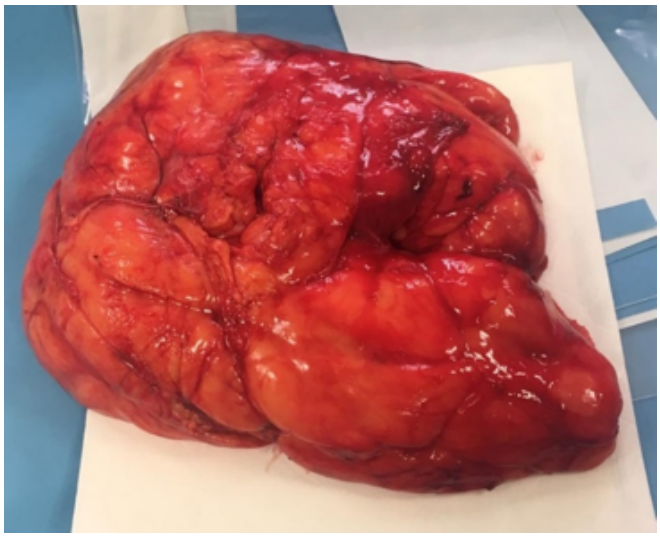

Figure 3. Postoperative view of the surgical specimen.

In the pathological and immunohistochemical examination, macroscopically 22x18x9 cm encapsulated fatty tissue was reported as thymolipoma. No postoperative complications were observed and the patient was discharged uneventfully. Besides, dyspnea symptom resolved completely after surgery. During the asymptomatic 9-month follow-up period, no recurrence was encountered.

Discussion

Thymolipoma is a very rare, slow-growing benign anterior mediastinal neoplasm that accounts for 2-9% of all thymic neoplasms. It is a well-circumscribed, and encapsulated lesion composed of mature adipose tissue containing islands of non-neoplastic thymic tissue. These tumors usually consist of adipose tissue, but also contain a small amount of thymic structure [2]. The amount of thymic tissue is in excess of what would be considered normal for patient's age. It is difficult to distinguish between lipoma and thymolipoma having fat component excess. High power view of a thymolipoma showing thymic elements within mature adipose tissue. Most consider it to be a benign neoplasm; however, there is some controversy regarding its pathogenesis. In thymolipoma, thymic epithelial elements can be detected by serial sectioning and immunohistochemical staining with cytokeratin [5].

Very slowly growing thymolipoma can sometimes reach very large and giant sizes. It can be seen as a mass image that fills a hemithorax and extends to the opposite side [1-5]. The symptoms are usually caused by compression of adjacent intrathoracic organs and structures such as the heart, large vessels, lungs and bronchus. Dyspnea, chest pain, cyanosis, tachypnea are the most common symptoms [3]. Our patient with COPD was admitted to the hospital with complaints of bloody sputum and worsening dyspnea. On his second admission, he presented with increased dyspnea.

Due to body temperature and gravity, the mass of thymolipoma grows into the anterior and inferior mediastinal area. It can mimic diaphragm eventration by erasing diaphragm contours on side radiographs [2,5]. Therefore, diaphragmatic eventration was also considered in our case and the surgery was started via VATS. Detection of adipose tissue on thorax CT may be helpful in diagnosis. Operation planning can be performed with magnetic resonance imaging and digital subtraction angiography. In this way, the feeding arteries and venous return associated with large vessels can be determined before the operation [1]. Lipoma, liposarcoma, mediastinal lipomatosis, and congenital diaphragmatic hernia can be considered as a differential diagnosis [2]. In our case, Morgagni hernia was considered as a preliminary diagnosis in the evaluation by chest x-ray, but this diagnosis was excluded according to the results of advanced radiological examinations and left-sided localization of the lesion. We considered the mass was benign, so positron emission tomography (PET-CT) was not obtained.

Needle biopsy is not appropriate for diagnosis. Radiological methods for diagnosis often give an idea about the lesion, but surgical excision is necessary for both definitive diagnosis and treatment. Total excision is easy because the lesion is encapsulated and does not invade surrounding tissues [5].

Thoracotomy, sternotomy and VATS can be chosen according to the nature of the lesion. VATS can be performed for small lesions. Thoracotomy is preferred for lesions that fill almost all of the hemithorax, even though the mediastinal component is present. Although we started with VATS, conversion to thoracotomy was necessary for safe and complete removal of the lesion. No recurrence is expected after a complete resection of thymolipoma. Long-term follow-up is not necessary for these patients due to the good prognosis.

In conclusion, although rare, thymolipoma should be considered in the differential diagnosis of fat-containing lesions filling the thorax.

Declaration of conflicting interests

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

Funding

The authors received no financial support

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Current Thoracic Surgery

To cite this article: Mestan H, Sertbaş N, Yazgan S, Samancılar Ö, Üçvet A, Gürsoy S. Videothoracoscopic resection of a posterior mediastinal parathyroid adenoma in a patient with aberrant subclavian artery. Curr Thorac Surg 2020;5(1):50-53.

Case Report

Videothoracoscopic resection of a posterior mediastinal parathyroid adenoma in a patient with aberrant subclavian artery

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ABSTRACT

Approximately 25% of the patients have an ectopic location of the parathyroid gland. In some cases, hyperfunctional parathyroid glands may extend into the mediastinum that requires mediastinal surgical exploration. A 66 years old woman presented with fatigue and raised serum calcium and parathormone levels. Thorax computed tomography revealed a mediastinal mass and an aberrant right subclavian artery (ARSA) which is the most common vascular anomaly of the aortic arch was demonstrated. The mediastinal mass was evaluated in favor of parathyroid adenoma by parathyroid scintigraphy. Videothoracoscopic resection of the adenoma was performed safely.

Keywords: videothoracoscopy, parathyroid adenoma, aberrant subclavian artery

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Doi: 10.26663/cts.2020.00010
Received 18.11.2019 accepted 05.03.2020

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by elevated serum calcium and parathormone levels. Although parathyroid adenoma, which is the most common cause of PHPT, is mostly located in the parathyroid gland, it has an ectopic location in approximately 25% of the cases [1]. Due to the rare possibility of ectopic parathyroid adenoma, diagnosis may be a challenge which delays management. Locating ectopic adenoma is another difficulty for surgery. Therefore, keeping a high index of suspicion of patients with raised serum calcium and parathormone (PTH) levels are the key point for diagnosis.

Here, we aimed to present a patient with the coexistence of mediastinal parathyroid adenoma and aberrant right subclavian artery, which is the most common intrathoracic major arterial anomaly.

Case Report

A 66 years old woman was referred to our department with fatigue and raised serum calcium and PTH levels. The patient had no comorbid disease except hypertension. There was no family history of any endocrine disorder. Thorax computed tomography (CT) revealed a heterogeneous density solid mass of 35x20 mm between the anterior of the right aberrant subclavian artery and posterior trachea (Figures 1,2)

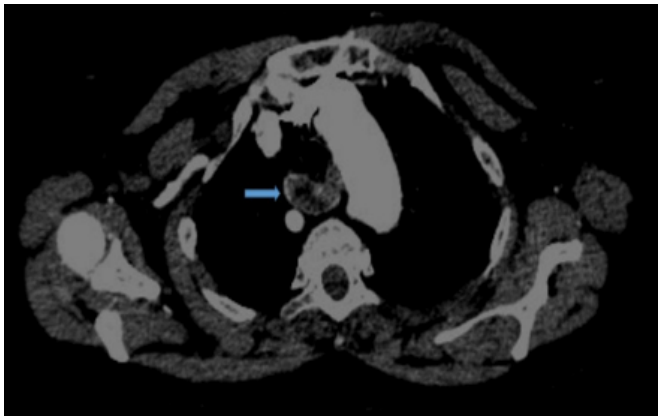

Figure 1. Thorax CT showing the parathyroid adenoma (arrow).

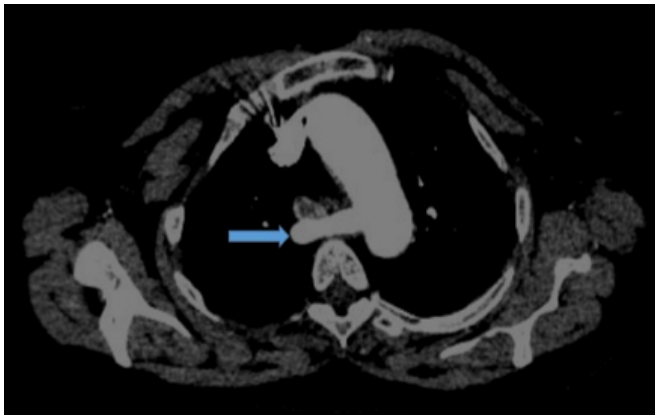

Figure 2. Thorax CT showing the aberrant right subclavian artery (arrow).

PTH level was 1225 pg/mL , serum calcium level was 11.4 mg/dL, and serum thyroid-stimulating hormone (TSH) value was 6.56 mIU/L. (The normal values for PTH, calcium and TSH is 15-65 pg/mL, 8.5- 10.5 mg/dL and 0.4-4 mIU/L respectively).

Parathyroid scintigraphy was performed with technetium 99, and the mass was evaluated in favor of parathyroid adenoma (Figure 3).

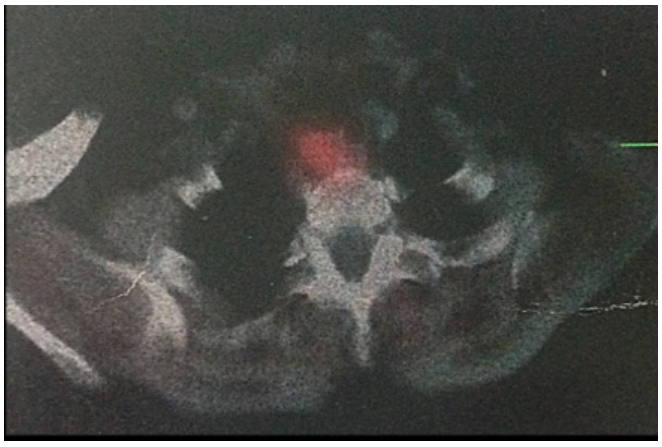

Figure 3. Parathyroid scintigraphy showing the lesion.

Based on these findings, mediastinal mass excision was performed via right videothoracoscopic approach. A utility port of 3 cm was placed at the fourth intercostal space at the anterior axillary line. One additional 1.5 cm port was then placed at the midaxillary line. After exploring the mediastinum, the parathyroid adenoma was identified between the anterior of the right aberrant sub-

clavian artery and posterior trachea. Using a harmonic scalpel, the parietal pleura was dissected while carefully avoiding the ARSA (Figure 4).

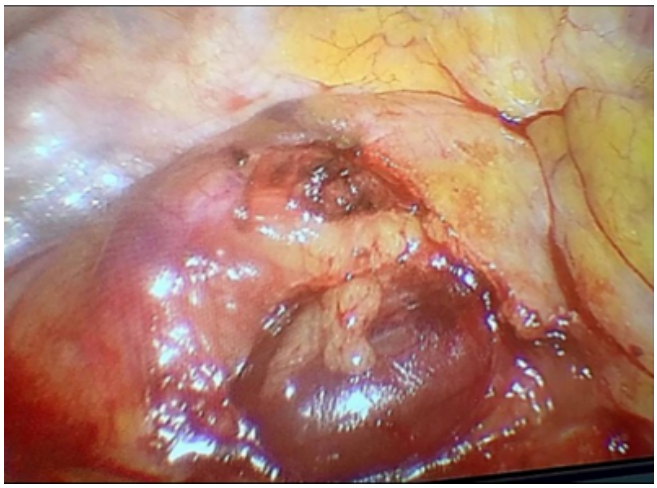

Figure 4. View during VATS: the parathyroid adenoma was identified between the anterior of the right aberrant subclavian artery and posterior trachea.

The parathyroid adenoma was then dissected free from the surrounding tissue. At the histopathological examination, the lesion with lobular appearance, dirty - yellow color and bleeding, was reported to be compatible with parathyroid adenoma. PTH level was 53.16 pg / mL and serum calcium level was 8.9 mg / dL on the first of postoperative day. The patient was discharged uneventfully at postoperative day 4.

Discussion

The most common cause of PHPT (80-85%), characterized by hypercalcemia and hypophosphatemia, is parathyroid adenoma [1]. It is generally seen in women around the age of 60 years old. As well as it may be asymptomatic, in some patients, osteoporosis, urinary stone, polyuria, vomiting can be seen.

It should be kept in mind that hyperparathyroidism may be a component of multiple endocrine neoplasia type 1 (MEN), pituitary tumor, and pancreatic islet tumor [2]. Although it is mostly located in the parathyroid gland, approximately 25% of the patients have an ectopic location [1]. Thymus (38%), retro / paraesophageal space (31%), thyroid (18%), mediastinum (6%), and carotid sheath (3%) are the most common sites of ectopic localization [3]. Ectopic inferior parathyroid glands are usually located in the anterior mediastinum within the thymus, while superior parathyroid glands are located in the posterosuperior mediastinum. Since the size is generally small, it is crucial to use preoperative technetium 99 (99mTc) scintigraphy for the localization.

Aberrant right subclavian artery (ARSA) or Lusoria artery is the most common vascular anomaly of the aortic arch with a rate of 0.5-2.5% [4]. It is a rare anatomical variation in which ARSA originates directly from the distal part of the aortic arch instead of brachiocephalic artery. Although it is mostly localized in the retroesophageal site, it may be located in anterior of the trachea or between the esophagus and trachea. The majority of cases with ARSA are asymptomatic. Retroesophageal form is the most commonly seen form that patients may complain of dysphagia due to compression of the esophagus. Anterior tracheal localization may be the cause of dyspnea. Surgery for ASA is offered in just case of being symptomatic.

99TC-MIBI scintigraphy is not a definite method but has a sensitivity of 80-90% [5]. False positivity may be detected in patients with lung cancer metastasis or patients with mediastinal tumors such as thymoma, seminoma, and lymphoma. False negativity may be seen in patients with multiple adenomas or hyperplasia [6]. Also, thoracic computed tomography (CT) and magnetic resonance imaging are helpful to determine the anatomic localization and the relationship of mediastinal parathyroid adenoma with the other structures.

CT can detect lesions over 1.5 cm in size. Although reviews are reporting that intraoperative gamma probes can be used for small-sized lesions [7], some surgeons suggest that this method will not be beneficial due to large vessels and heart activities [8]. Intravenous methylene blue is another option to localize ectopic glands. In some cases, intraoperative parathyroid hormone assay is used to be sure that the excised mass is a parathyroid adenoma or not.

The definitive treatment of parathyroid adenoma is surgery. Surgical methods such as cervical approach, video-assisted mediastinoscopy, sternotomy, thoracoto-

my, video thoracoscopy should be chosen according to the location of the mass. The cervical approach is the preferred method for adenomas located at or above the aortic arch level. Thoracotomy, sternotomy, mediastinotomy, or video thoracoscopy (VATS) is more appropriate for lesions located under the aortic arch or deeper in the mediastinum [9]. Parathyroid adenoma excision using video thoracoscopy was first reported in 1994 by Prinz et al. Subsequently, it is reported that VATS is a feasible and safe approach for mediastinal parathyroid adenoma [10]. Since then, video thoracoscopy has been used more widely. VATS offers more advantages over both thoracotomy and sternotomy. It allows better visualization of the tumor and exposure of the mediastinum, excellent access, shorter operative time, shorter tube dwell time, shorter hospital stay and reduced postoperative pain. Also it is superior in the cosmetic way when compared to sternotomy and thoracotomy scars [11]. Complications such as pleural effusion, hematoma, pneumothorax, wound site infection, mediastinitis, and sternal dehiscence are more likely to be seen in conventional methods like sternotomy and thoracotomy.

In conclusion, videothoracoscopic resection of mediastinal masses can be performed safely even in patients with aberrant vascular structure.

Declaration of conflicting interests

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

Funding

The authors received no financial support.

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All tables and figures must be numbered consecutively as they are referred to in the text. Please refer to tables and figures 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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