ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2021:28(4):551-558 doi: 10.17343/sdutfd.753812

CLINICAL AND RADIOLOGICAL EVALUATION IN RARE PRIMARY MALIGNANT TUMORS OF THE LUNG

AKCİĞERİN NADİR PRİMER MALİGN TÜMÖRLERİNDE KLİNİK VE RADYOLOJİK DEĞERLENDİRME

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Cite this article as: Öz G, Özdemir Ç, Aydın S, Dumanlı A, Günay E, Çilekar Ş, Günay S, Gencer A, Öztürk D, Demirağ F. Clinical and Radiological Evaluation in Rare Primary Malignant Tumors of the Lung. Med J SDU 2021; 28(4): 551-558.

Öz

Amaç

Akciğerin en sık görülen primer malign tümörlerini yassı hücreli karsinom, küçük hücreli karsinom ve adenokarsinom oluşturur. Ancak, nadir görülen bazı malign primer akciğer tümörleri de akciğeri etkileyebilir, tanı ve tedavide zorluklara neden olabilir. Geleneksel görüntüleme yöntemleri olguların birçoğunda tanıda yeterince yardımcı olmaz hatta preoperatif alınan doku örnekleri tanı koymada yetersiz kalabilir. Endobronşial lezyonu olan vakalarda örneklerin küçük olması veya endobronşial lezyon olmayan santral tümörlerde transtorasik biyopsi yapılamaması tanıyı zorlaştırabilir. Kesin tanı ancak operasyon sonrası alınan daha büyük doku örnekleri ile ayrıntılı incelemeler sonunda konabilir. Ayrıca frozen incelemesinde benign-malign ayrımı yapılamaması cerrahın yapacağı rezeksiyonu olumsuz yönde etkileyebilir. Eksik ya da gereksiz rezeksiyona neden olabilir. Çalışmamızın amacı literatürde çok az bildirilen bu tümörlerin klinik radyolojik ve histopatolojik görünümlerini değerlendirerek tanı ve tedavilerine katkıda bulunmaktır.

Gereç ve Yöntem

2010-2019 yılları arasında kliniğimizde opere edilen oldukça nadir 10 malign primer akciğer tümörü hasta çalışmaya dahil edildi. Tüm hastalar, yaş, cinsiyet, semptomlar, preoperatif görüntüleme yöntemleri ve invazif tanı yöntemleri ile retrospektif olarak incelendi. Tümör lokalizasyonu, tümör boyutları, yapılan cerrahi operasyon tipi ve yaşam süreleri kaydedildi.

Bulgular

Çalışmamıza 10 hasta dahil edildi. Hastaların 6 tanesi erkek, 4 tanesi kadındı. Yaş ortalamaları 53.4 idi. 3 hastaya sol alt lobektomi, 2 hastaya sol pnömonektomi, 3 hastaya wedge rezeksiyon, 1 hastaya sol üst lobektomi, 1 hastaya orta lobektomi yapıldı. Hastaların postoperatif histopatolojik tanıları 2 hastada karsinosarkom, 2 hastada büyük hücreli nöroendokrin karsinom, 2 hastada epiteloid hemanjioendotelyoma, 1 hastada glomanjiosarkom, 1 hastada primer pulmoner leiomyosarkom, 1 hastada mukoepidermoid karsinom, 1 hastada sinovyal sarkom olarak raporlandı.

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Müracaat tarihi/Application Date: 17.06.2020 • **Kabul tarihi/Accepted Date:** 06.08.2020
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Sonuç
Akciğerin nadir görülen primer malign tümörlerine preoperatif görüntüleme ve invaziv yöntemler ile tanı koymak zor olabilir. Ameliyat öncesi yapılan tomografi eşliğinde ince iğne biyopsi, tru-cut biyopsi, bronkoskopik biyopsi örnekleri ve frozen incelemeleri tanı koymakta yetersiz kalabilir. Bu durum, operasyonu yapacak cerrahı yapılacak akciğer rezeksiyonu konusunda yanlış yönlendirebilir.

Anahtar Kelimeler: Nadir Primer Akciğer Tümörleri, Malign, Glomanjiosarkom, Epiteloid Hemanjioendotelyoma

Abstract

Objective
The most common primary malignant tumors of the lung are squamous cell carcinoma, small cell carcinoma and adenocarcinoma. However, some rare malignant primary lung tumors can also affect the lung and cause difficulties in diagnosis and treatment. Conventional imaging methods do not help the diagnosis in most cases, and moreover, preoperative tissue samples may fail to establish a diagnosis. In cases with endobronchial lesions, small samples or lack of transthoracic biopsy in central tumors without endobronchial lesions can make diagnosis difficult. The definitive diagnosis can only be made after larger examinations with larger tissue samples taken after the operation. In addition, failure to differentiate benign-malignant in frozen examination may negatively affect the resection of the surgeon. It can cause incomplete or unnecessary resection.

The aim of this study was to evaluate the clinical radiological and histopathological features of these tumors, which have been rarely reported in the literature, and to contribute to the diagnosis and treatment of these tumors.

Material and Methods
The study included 10 patients with rare malignant primary lung tumor who were operated on in our clinic between 2010 and 2019. All patients were retrospectively evaluated in respect of age, gender, symptoms, preoperative imaging methods and invasive diagnostic methods. Tumor localization, tumor size, type of surgical operation and survival were recorded.

Results
The 10 patients included in the study comprised 6 males and 4 females. Postoperative histopathological diagnoses of the patients were reported as 2 carcinosarcomas, 2 large cell carcinomas, 2 epithelioid hemangioendothelioma, 1 glomangiosarcoma, 1 primary pulmonary leiomyosarcoma, 1 mucoepidermoid carcinoma, and 1 synovial sarcoma.

Conclusion
It can be difficult to diagnose in rare primary malignant lung tumors by preoperative imaging and preoperative invasive diagnostic methods. CT-guided fine needle biopsy and tru-cut biopsy, endobronchial biopsy and frozen samples performed before surgery may be insufficient in diagnosis, which may mislead the surgeon about lung resection.

Keywords: Rare Primary Lung Tumors, Malignant, Glomangiosarcoma, Epiteloid Hemangioendothelioma

Introduction

Squamous cell carcinoma, adenocarcinoma and small cell carcinoma account for approximately 90% of all lung tumors. Other tumors can be classified as rare and very rare tumors. They may originate from many other cell types which include epithelial, salivary gland, hemotopoietic system or mesenchymal cells (1). Preoperative radiological examinations are not usually helpful in the diagnosis of very rare malignant primary lung tumors. Bronchoscopic examination may not be sufficient for differential diagnosis even in cases where localization is appropriate. During frozen examinations, the pathologist may have difficulty in distinguishing benign or malignant. In this study, a group of malignant primary lung tumors, which are rarely reported in the lung and were treated with surgery, are presented in the light of the literature.

Material and Methods

Our study was approved by the Clinical Research Ethics Committee of University (05.06.2020/Approval no: 220). A retrospective analysis was made of 10 rare malignant primary lung tumors operated on in our clinic, between 2010 and 2019. All patients were evaluated in terms of age, gender, symptoms, tumor size and localization, diagnostic radiological examinations, preoperative pathology, type of operation, postoperative pathological results and survival and follow-up period. All patients underwent routine laboratory tests, electrocardiography, pulmonary function tests, and thorax tomography.

Cranial computed tomography (CCT) or MRI was performed on patients preoperatively diagnosed with malignancy. Fiberoptic bronchoscopy was performed in

all patients, and in 5 patients, PET-CT was performed preoperatively. One patient underwent CT-guided fine needle biopsy but result were not diagnostic (Figure 7a). 1 patient did not accept this procedure.

CT-guided needle biopsy could not be performed in 1 patient due to the small size of the lesion (Figure 5a) and in 1 patient it was not performed because of the lesion localization was suitable for total excision with videothoracoscopy (Figure 4 a).

Results: The 10 patients included in the study comprised 6 males and 4 females with a mean age of 54.3 years (range, 17-72 years). Complaints on admission to hospital were hemoptysis in 4 patients (40%), cough in 4 patients (40%) and dyspnea in 2 patients (20%). Four patients (40%) had a history of smoking. The postoperative pathological diagnoses of the 10 patients operated on were carcinosarcoma in 2 patients (20%) (Figure 1 b-c), glomangiosarcoma in 1 patient (10%) (Figure 2b-c), primary pulmonary leiomyosarcoma (10%) (Figure 3b-c), epithelioid hemangioendothelioma in 2 patients (20%) (Figure 4b-c), large cell neuroendocrine carcinoma in 2 patients (20%) (Figure 5b-c), mucoepidermoid carcinoma in 1 patient (10%) (Figure 6b-c) and synovial sarcoma (10%) in 1 patient (Figure 7b-c). Glomangiosarcoma, one case of carcinosarcoma, primary pulmonary leiomyosarcoma, mucoepidermoid carcinoma and 1 large cell neuroendocrine carcinoma were observed to have central localization on thorax tomography (Figures 1a, 2a, 3a, 5a, 6a). One carcinosarcoma, 2 pulmonary epithelioid hemangioendothelioma, and 1 large cell neuroendocrine carcinoma were seen to have peripheral localisation (Figures 1b, 4a, 5b, 7a). The largest tumor size was 8x8 cm in diameter. The SUVmax value on PET-CT was highest in mucoepidermoid carcinoma (SUVmax:9.9) and lowest in

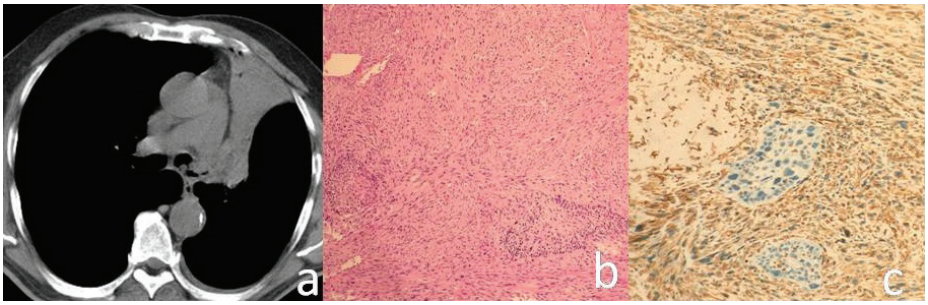

Figure 1
Figure 1a :Tumor invading the left main bronchus.
Figure 1b :The mitotic-rich mesenchymal component with spindle-nucleated cytoplasm and the other second component (x100 HE) consisting of malignant epithelial cells intertwined with this component .
Figure 1c :The tumor had a positive reaction with vimentin in the mesenchymal component and a negative reaction in the epithelial component.

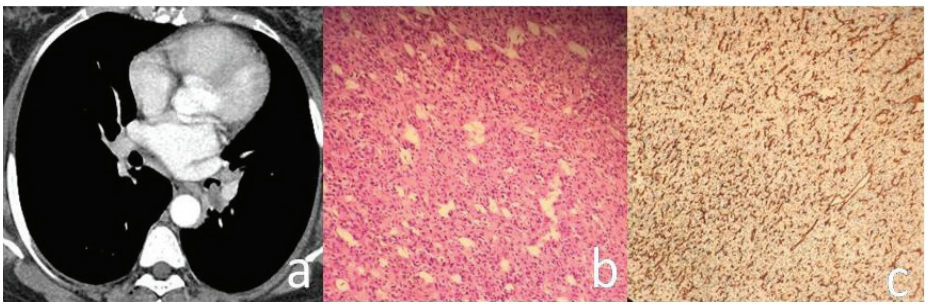

Figure 2
Figure 2 a :Tumor seen to have caused atelectasis in the left lower lobe.
Figure 2 b :Tumor (x100 HE) composed of clear cytoplasmic cells with atypical nuclei, partially aligned around the vascular structures and partially not forming a pattern.
Figure 2 c: Strong CD34 immune reactivity seen in the vascular structures within the tumor, but no reaction in the tumor cells.

epithelioid hemangioendothelioma (SUV max: 1.4). Endobronchial lesion was detected in 7 patients who underwent preoperative bronchoscopy. Bronchoscopic biopsy revealed hemangioma in 2 patients, squamous cell carcinoma in 1 patient, non-small cell lung cancer (NSCLC) in 1 patient, and mesenchymal tumor in 1 patient (Table 1). The types of operation performed are outlined in Table 2. The stages of the operated patients ranged from stage 1A to stage 4A. Mediastinoscopy was performed in 5 patients. In a carcinosarcoma with left pneumonectomy and synovial sarcoma with wedge resection, the tumor was at the resection margin. Of the total 10 patients, 10 received only adjuvant chemotherapy and 3 received adjuvant chemotherapy and radiotherapy. The mean follow-up period of the operated patients was 20.3 months. A patient with large cell neuroendocrine carcinoma who underwent left pneumonectomy died 6 months after the operation due to acute myocardial infarction. The patient with glomangiosarcoma died 14 months after the operation and the patient with synovial sarcoma died 3 months later due to disease progression. Of the 10 patients, 7 are still alive (Table 2).

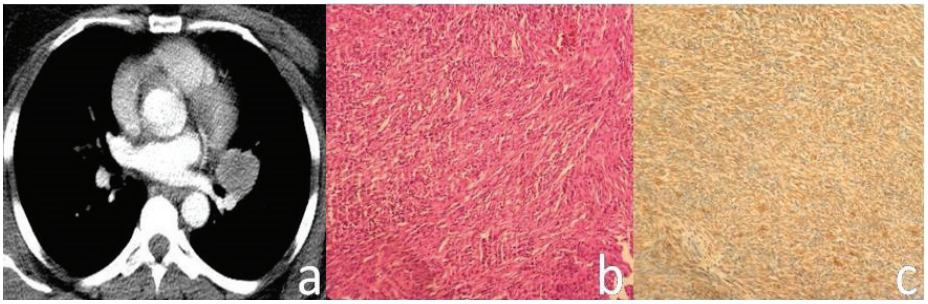

Figure 3
Figure 3 a : Tumor has a smooth edge but has invadeds the lingular artery.
Figure 3 b : Tumor consisting of spindle nucleus cells with spindle cytoplasm (x100 HE), which are parallel to each other in cellular nature, forming vertically intersecting bundles.
Figure 3 c : Reactivity of diffuse cytoplasmic vimentin in the tumor .

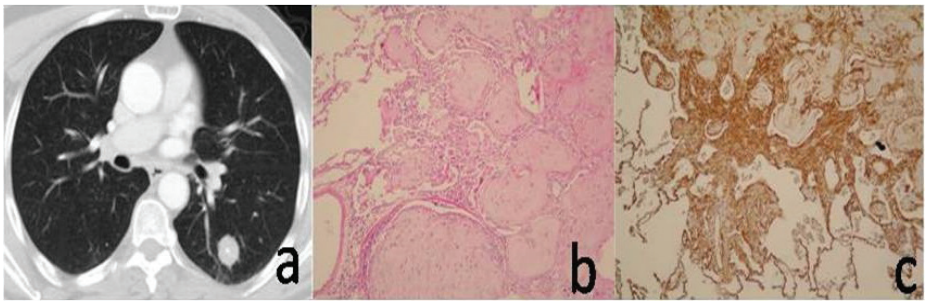

Figure 4
Figure 4 a: Central calcified tumor mimicking a benign tumor.
Figure 4 b: Myxoid stroma filling alveolar lumens settled atypical cells (HEX100)
Figure 4 c: CD31 positivity in tumor cells (CD31X40).

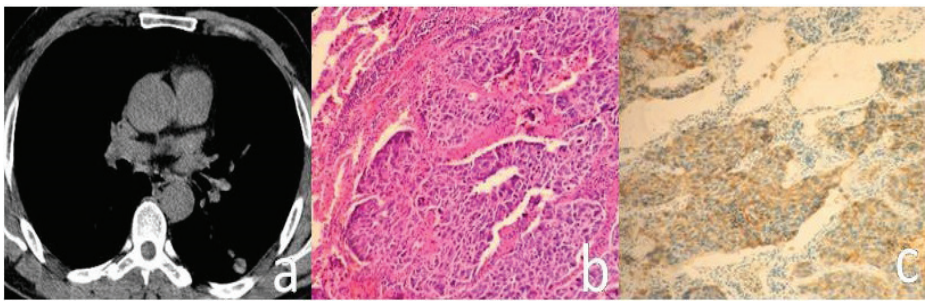

Figure 5
Figure 5 a: Peripheral tumor with satellite nodule.
Figure 5 b :Tumor islands (x200 HE), composed of nucleated prominent syncyteal cells with numerous mitosis, showing necrotic, peripheral palisation.
Figure 5 c :Membrane-stoplasmic CD56 immunoreactivity in tumor cells.

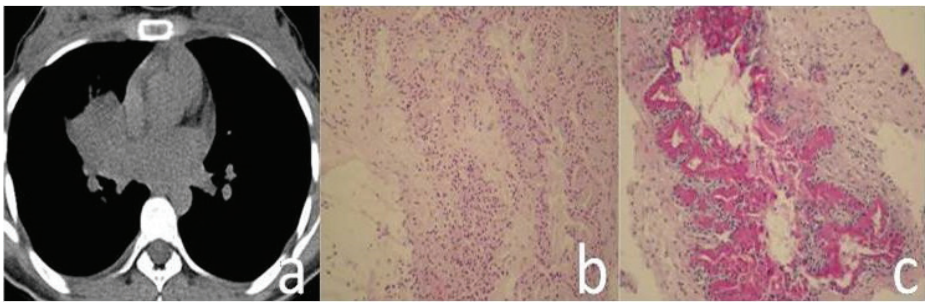

Figure 6
Figure 6a :Middle lobe atelectasis induced tumor.
Figure 6 b :Glandular structures and squamoid cells lined with mucinous cells (HE X 200).
Figure 6 c :Mucin positivity in glandular structures (mucin carminX100)

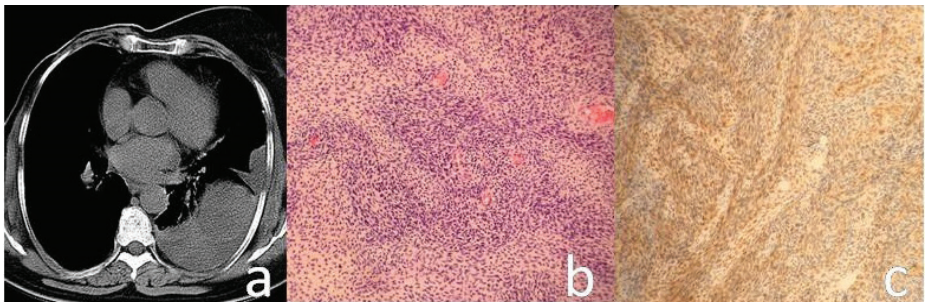

Figure 7
Figure 7a: Tumor causing left lower lobe consolidation .
Figure 7b: Monophasic tumor (x 100 HE) consisting of spindle nuclei forming a storiform pattern in some hypocellular and cellular areas).
Figure 7c :Diffuse cytoplasmic Bcl-2 immunoreactivity in tumor cells.

Table 1 Demographic Futures Of Patient's And Tumor Characteristics

Tumor Type	Age	Gender	Symptom	Smoking	Tumor Size	Localization	Preoperative Diagnosis	Pet Ct(Suv-Max)	Ebl
CS	67	M	Hemoptysis	(-)	3*3	Central	Squamous cell ca insutu	14.1	(+)
CS	66	M	Cough	(+)	8*8	Peripheral	(-)	(-)	(+)
GLS	53	F	Hemoptysis	(+)	4*3	Central	Hemangioma	5.4	(+)
LMS	48	F	Hemoptysis	(+)	4*4	Central	Hemangioma	(-)	(+)
PEH	72	M	Hemoptysis	(-)	4*3	Peripheral	(-)	1.4	(-)
PEH	27	M	Cough	(-)	Multıple nodules	Peripheral	(-)	(-)	(-)
LCNEC	58	M	Cough	(-)	2*2	Peripheral	(-)	3.8	(+)
LCNEC	66	M	Cough	(+)	3*3	Central	Non-small cell ca	(-)	(+)
MEC	17	F	Dyspnea	(+)	4*4	Central	Mesenchymal tumor	9.9	(+)
SS	60	F	Dyspnea	(-)	3*3	Peripheral	(-)	(-)	(-)

TABLE 1 ABBREVIATIONS : CS: Carcinosarcoma ; GLS: Glomangiosarcoma LMS: Leiomyosarcoma ; PEH: Pulmonary Epitelioid Hemangioendotelioma ; LCNEC: Large cell neuroendocrin carcinoma MEC: Mucoepidermoid carcinoma SS: Snovyval sarcoma EBL:Endobronchial Lesion

Table 2 Operations, Stages And Follow Up

Tumor Type	Age	Gender	Symptom	Smoking	Tumor Size	Localization	Preoperative Diagnosis	Pet Ct(Suv-Max)	Ebl
CS	67	M	Hemoptysis	(-)	3*3	Central	Squamous cell ca insutu	14.1	(+)
CS	66	M	Cough	(+)	8*8	Peripheral	(-)	(-)	(+)
GLS	53	F	Hemoptysis	(+)	4*3	Central	Hemangioma	5.4	(+)
LMS	48	F	Hemoptysis	(+)	4*4	Central	Hemangioma	(-)	(+)
PEH	72	M	Hemoptysis	(-)	4*3	Peripheral	(-)	1.4	(-)
PEH	27	M	Cough	(-)	Multıple nodules	Peripheral	(-)	(-)	(-)
LCNEC	58	M	Cough	(-)	2*2	Peripheral	(-)	3.8	(+)
LCNEC	66	M	Cough	(+)	3*3	Central	Non-small cell ca	(-)	(+)
MEC	17	F	Dyspnea	(+)	4*4	Central	Mesenchymal tumor	9.9	(+)
SS	60	F	Dyspnea	(-)	3*3	Peripheral	(-)	(-)	(-)

TABLE 2 ABBREVIATIONS : CS: Carcinosarcoma ; GLS: Glomangiosarcoma LMS: Leiomyosarcoma ; PEH: Pulmonary Epitelioid Hemangioendotelioma ; LCNEC: Large cell neuroendocrin carcinoma MEC: Mucoepidermoid carcinoma SS: Snovyval sarcoma ADJ KT: Adjuvant chemotherapy ADJ.RT: Adjuvant radiotherapy M.copy: Mediastinoscopy L.N Met: Lymph nod metastasing

Discussion

Almost all primary lung tumors are composed of carcinomas and <1% are other histological types. Of all lung cancers, 28-42% are adenocarcinoma, 25-44% are squamous cell carcinoma, 20% are small cell carcinoma and 1-2% are carcinoid tumors. Rare tumors of the lung comprise <2% (2).

The incidence of large cell neuroendocrine carcinoma (LCNEC) varies between 2.1-3.5% and is thought to be actually higher because it is difficult to diagnose (3-7). There is no specific image on radiographic examinations. Most lesions are a peripheral mass. Immunohistochemically they release chromogranin, neuron-specific enolase, synaptophysin, and somatostatin (3).

Carcinosarcomas constitutes 0.3-1.3% of all lung tumors. Although the lesions are both central and peripheral, centrally located lesions are more frequently observed (8). The most common epithelioid component is squamous cell carcinoma, while the sarcomatoid component is rhabdomyosarcoma (9, 10). In contrast to the literature, the predominant component was leiomyosarcoma in the current study patients. Calcification in metastasis is not found in NSCLC, but it is more common in carcinosarcomas (8) In the absence of fibroblasts in the mesenchymal component, it is distinguished from the spindle cell carcinoma group (11,12).

Pulmonary epithelioid hemangioendotheliomas (PEHs) of the lung are extremely rare vascular mesenchymal tumors. PEHs follow a low to moderate course between the hemangioma and the angiosarcoma cell types (13). Liver and lung metastases are the most common, with a lower rate than angiosarcoma (14). There was no metastasis at the time of diagnosis in both of the current cases. The prognosis of the tumor ranges from 1 year to 30 years and spontaneous regression of asymptomatic cases is

quite interesting (15,16). Differential diagnosis of PEH should be made with granulomatous and metastatic lung diseases, especially those with bilateral multiple nodular form (17,18). Histologically, they appear as a hyalinizing center surrounded by a cellular margin extending to the alveoli and vessels, and contain sealed ring-shaped fibromyxoid epithelioid cells with abundant cytoplasm. Although this appearance is found in adenocarcinoma and mesothelioma, immunohistochemical analysis allows differentiation (19,20).

Mucoepidermoid carcinomas (MECs) are slowly-growing malignant tumors from the submucosal glands. MECs of the tracheobronchial tree constitute 0.3% of primary lung tumors (21). These tumors are usually central tumors and originate from the main bronchus, lobes and segment bronchi. Therefore, radiological consolidation and pneumonic infiltration findings are quite common and the diagnosis may be confused with asthma (22). In the current patient diagnosed with MEC, the tumor completely occluded the middle lobe and was treated with a preliminary diagnosis of middle lobe pneumonia.

In a study performed by Li et al., 21 of 24 patients operated on for MEC had centrally located lesions and the majority were <3 cm in diameter (23). Calcification rates in lesions vary between 9-50% (24, 25). In the current study case, no significant calcification was observed on thorax CT. A definitive diagnosis is made from mucin carmine staining positivity in glandular structures, keratin 5/6 positivity in tumor cells and P40 positivity in squamous cells (26,27).

Glomus tumors are benign neoplasms originating from glomus bodies in extremities. Very few reports of glomangiosarcoma have been reported that originated from visceral organs such as the stomach, kidney, and lungs. It is most commonly seen in the trachea within the respiratory system (28). Surgical treatment is the treatment of choice in patients who do not have metastasized tumors (29,30).

Primary pulmonary leiomyosarcoma (PPL) is a very rare tumor of primary lung malignancy with an incidence of<0.5% (31). PPL originates from smooth muscle cells in the lung parenchyma, bronchus, and pulmonary artery, respectively. The current case had bronchial origin and invaded the lingular artery. Radiologically, the tumor appears as oval lesions with smooth borders (32). Immunohistochemical staining excludes other tumors. Despite the negativity of Desmin and Calponin, strong staining with Vimentin, H-Caldesmon, α-SMA, and HHF35 indicates that the tumor is of smooth muscle origin (33).

Synovial sarcomas constitute approximately 2% of soft tissue tumors seen in people over 50 years of age. It is a highly aggressive tumor (34). It is usually located in the central region causing hemoptysis, while those in the peripheral regions are less invasive to the surrounding tissues (35,36). Although adjuvant chemotherapy is effective in prolonging survival, the prognosis is poor in synovial sarcoma (37). Since the current study patient had advanced disease, this treatment option was applied.

This study has some limitations, primarily the small number of the population. Other limitations were that CT and PET-CT were not performed in a single center, and that not all patients received PET-CT. Another limitation is that CT-guided fine needle biopsy or trucut biopsy could not be performed on all peripheral lesions.

In our study, all patients underwent fiberoptic bronchoscopy. All of the pathology results obtained after bronchoscopy were different from the postoperative pathology results. CT-guided fine needle biopsy result was also not diagnostic. In addition, the pathology of the frozen specimen in the patient with glamanjiosarcoma was interpreted as benign (hemangioma).

In conclusion, primary malign rare tumors of the lung are difficult to diagnose with preoperative diagnostic methods and biopsy specimens. Although some of these tumors are malignant, they mimic benign lesions with their smooth shape on tomography and low FDG uptake on PET-CT. As the distinction between benign and malignant is difficult in frozen examinations, this may cause difficulties in resection selection. Diagnosis can only be made with gross material and very detailed histopathological examinations. As the number of cases in the literature increases, diagnosis and treatment will become easier.

Conflict of interests

The authors have no conflict of interests to declare in association with the present study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Ethical Approval

Our study was approved by the Clinical Research Ethics Committee of Afyonkarahisar Health Science University (05.06.2020/Approval no: 220).

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