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Is thoracic CT adequate for diagnosis and differential diagnosis in patients with pleural thickening?

Plevral kalınlaşması olan hastaların tanı ve ayırıcı tanısında Toraks BT yeterli midir?

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SUMMARY

Objective: Lung pathologies associated with pleural thickening are presented along with similar clinical and radiological findings. The present study highlights the importance of the differential diagnosis verification of patients with pleural thickening. Video-assisted thoracoscophic surgery (VATS) is one of the most common diagnostic and therapeutic method used for this purpose. In this study, we aim to deliver our clinical investigation results on patients diagnosed with pleural pathology in the light of recent literature.

Method: In this study, data of 40 patients that were applied single-port VATS pleural biopsy in our clinic between May 2012 and June 2014 were retrospectively assessed. Thoracic CT and pathology results were compared. Clinical diagnosis, radiologic findings, and biopsy results were evaluated retrospectively.

Results: The average age of the patients is 59.15 ±12.13 (age range 23, 82). There was an environmental exposure to asbestos in 14 patients (35%). Twenty-five patients (62.5%) were followed-up with the diagnosis of mesothelioma with clinical and radiological findings, 8 patients (20%) of tuberculosis, 4 patients (10%) of pleural metastasis and 3 patients (7.5 %) of pleuritis. Histopathologically 8 patients (20%) were diagnosed with malignant mesothelioma, 1 patient (2.5 %) was localized fibrous tumor, 2 patients were (5%) diagnosed with reactive mesothelial hyperplasia, 6 patients (15%) were malignant epithelial tumor metastasis, 16 patients (40%) were fibrinous pleuritis, 6 patients (15%) were chronic granulomatous inflammation, and 1 patient (2.5%) was chronic lymphocytic inflammation.

Conclusions: The present study demonstrates insufficiency of thoracic CT for diagnosis and differential diagnosis due to similar clinical and radiological findings associated with pathological pleural thickening. Histopathologic examination is required for diagnosis. However, thoracic CT is still a method of radiographic imaging that is actively used in determination of pleural biopsy position, evaluation, and clinical monitoring of response to treatment.

Keywords: Fibrinous pleuritis, chronic granulomatous reaction, mesothelioma, pleural thickening, thoracic CT

ÖZET

Amaç: Plevral kalınlaşma ile ilişkili akciğer patolojileri benzer klinik ve radyolojik bulgular göstermektedir. Bu çalışmada, plevral kalınlaşması olan hastaların ayırıcı tanısının yapılmasının önemini vurgulamaktadır. Bu amaçla en yaygın kullanılan tanı ve tedavi yöntemi video yardımlı torakoskopik cerrahi (VATS)'dır. Bu çalışmada, plevral kalınlaşması olan hastalarda klinik araştırma sonuçlarımızı güncel literatür ışığında sunmayı amaçladık.
Yöntem: Mayıs 2012-Haziran 2014 tarihleri arasında kliniğimizde tek port VATS plevral biyopsisi uygulanan 40 hastanın verileri retrospektif olarak değerlendirildi. Torasik BT ve patoloji sonuçları karşılaştırıldı. Klinik tanı, radyolojik bulgular ve biyopsi sonuçları retrospektif olarak değerlendirildi.
Bulgular: Hastaların yaş ortalaması 59,15 ± 12,13'tü (yaş aralığı 23-82). 14 hastada (%35) çevresel asbest maruziyeti vardı. Klinik ve radyolojik bulgularına göre, 25 hasta (%62,5) mezotelyoma, 8 hasta (%20) tüberküloz, 4 hasta (%10) plevral metastaz ve 3 hasta da (%7,5) plörit ön tanısı ile takip edildi. Histopatolojik olarak ise 8 (%20) malign mezotelyoma, 1 (%2,5) lokalize fibröz tümör, 2 (%5) reaktif mezotel hiperplazisi, 6 (%15) malign epitelyal tümör metastazı, 16 (%40) fibrinöz plörit, 6 (%15) kronik granülomatöz inflamasyon ve 1 hastada da (%2,5) kronik lenfositik inflamasyon saptandı.
Sonuç: Bu çalışma, benzer klinik ve radyolojik bulgulara bağlı olarak plevral kalınlaşma ile ilişkili hastalıklarda toraks BT'nin tanı ve ayırıcı tanıda yetersiz olduğunu göstermektedir. Tanı için histopatolojik inceleme gereklidir. Bununla birlikte toraks BT, halen plevral biyopsi yerinin belirlenmesinde, değerlendirilmesinde ve tedaviye yanıtın klinik olarak izlenmesinde aktif olarak kullanılan bir radyografik görüntüleme yöntemidir.
Anahtar sözcükler: Fibrinöz plörit, kronik granülomatöz reaksiyon, mezotelyoma, plevral kalınlaşma, toraks BT.

INTRODUCTION

Pathologies associated with pleural thickening are presented with similar clinical and radiological findings[1]. Therefore, it is very important to perform differential diagnosis of patients with pleural thickening. VATS (Video-assisted thoracoscophic surgery) is one of the most common diagnostic and therapeutic method used for this purpose[1-3]. In this study, we aim to analyze our patients with pleural pathology who diagnosed with history, physical examination, radiology and VATS findings, retrospectively.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of our university (Letter no: 2016-04/15). During the period of May 2012-June 2014 single port VATS pleural biopsies were performed in 40 patients (25 male, 15 female) in Sivas Numune Hospital. Pre-biopsy clinical diagnosis, radiologic findings, biopsy results, follow-up clinical and radiological findings were evaluated, retrospectively.

Multidetector Computed Tomography (MDCT) was performed with a 16-detector-row CT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). Scans were obtained with collimation of 10 mm and a pitch ratio of 1:1.5 in all patients. Iodinated contrast medium (90 mL; Omnipaque; Amersham Health, Cork, Ireland) was injected intravenously at 4.5 mL/s. All the images were reevaluated by the same radiologist to prevent discrepancy.

A single-port VATS pleural biopsy was done for all of the patients in the lateral decubitus position under general anesthesia after the preoperative preparations were completed. Input region have been identified according to pleural thickening localization guided on thoracic CT. After the procedure, a single chest tube is placed from the entrance port, and the operation is terminated.

Immunohistochemical analysis was performed for histopathological diagnosis (like EMA, CK7, CK19, Calretinin, HBME-1, CK5/6, TTF-1, mCEA, CK20). Streptavidin biotin immune-histochemical study on paraffin embedded blocks was done with Bond Max Leica equipment accompanied by appropriate controls. When planning the study, the same pathologist evaluated all the blocks again.

RESULTS

The mean age of the patients was 59.15 (range 23-82 years). The majority of patients (n=14, 35%) were from Yıldızeli, a rural region of Sivas with high risk of asbestos exposure. Only nine patients have smoking history of 10 to 20 years. The total of 40 patients included in our study and their clinical history is as follows: 25 of them (62.5%) were diagnosed with mesothelioma, 8 of them (20%) with tuberculosis, 4 of them (10%) with pleural metastasis, and 3 of them (7.5%) with fibrinous pleuritis. Histopathologically, the diagnosis were malignant mesothelioma in eight (20%) of the patients localized fibrous tumor in one patient (2.5%) reactive mesothelial hyperplasia in

two patients (5%), malignant epithelial tumor metastasis in six patients (15%), fibrinous pleuritis in 16 patients (40%), chronic granulomatous inflammation in six patients (15%) and chronic lymphocytic inflammation in one patient (2.5%). The demographic characteristics of the patients are illustrated in Tables 1 and 2.

Table1. The demographic characteristics of the patients.

	Number of patients (%)
Female	15 (37.5)
Male	25 (62.5)
Environmental asbestos exposure	14 (35)
Smoking (10-20 packets/year)	9 (22.5)
Clinic pre-diagnosis	
Malignant mesothelioma	25 (62.5)
Tuberculosis	8 (20)
Pleural metastasis	4 (10)
Fibrinous pleuritis	3 (7.5)
Histopathological diagnosis	
Fibrinous pleuritis	16 (40)
Malignant mesothelioma	8 (20)
Chronic granulomatous inflammation	6 (15)
Malignant epithelial tumor metastasis	6 (15)
Reactive mesothelial hyperplasia	2 (5)
Localized fibrous tumor	1 (2.5)
Chronic lymphocytic inflammation	1 (2.5)

Table 2. MDCT characteristics of the patients.

	MM	**FP**	**CGI**	**MET**	**RMH**	**CLI**	**LFT**
Pleural thickness	8	15	6	6	2	1	1
Pleural effusion	7	11	3	4	1	-	1
Mediastinal Pleural thickness	5	6	1	2	1	1	1
Inter-lobar fissure involvement	7	13	4	5	2	1	1
Loss of lung volume	6	10	3	4	2	-	1
Calcified pleural plaque	3	7	3	-	1	-	1
Mediastinal lymphadenopathy	2	1	1	1	-	-	-
Chest wall invasion	1	1	1	2	-	-	-

MM (Malignant Mesothelioma), **FP** (Fibrinous Pleuritis), **CGI** (Chronic Granulomatous Inflammation), **MET** (Malignant Epithelial Tumor Metastasis), **RMH** (Reactive Mesothelial Hyperplasia), **CLI** (Chronic Lymphocytic Inflammation), **LFT** (Localized Fibrous Tumor).

Thoracic CT of eight patients diagnosed with malignant mesothelioma showed pleural effusion in seven cases, pleural thickening in eight patients, mediastinal pleural thickening in five patients, interlobar fissure thickening in seven patients, and lung volume reduction in six patients (Figure 1a). Diffuse pleural thickening was often concentric and nodular. Pleural effusion was usually unilateral. Calcified pleural plaques are also revealed in three patients. In this group, three patients were evaluated with epithelioid subtype. Pathological investigation showed malign epithelial tumor with atypical cells. The aforementioned cells are distinguished with their hyperchromatic nuclei, distinctive nucleoli, and eosinophilic cytoplasm. The nucleus of some tumor cells are also positioned on periphery.

Immunohistochemical examination was performed for differential diagnosis of the tumoral foci. Cytoplasmic staining with CK 7, CK 5/6 and calretinin and membranous staining with HBME-1 and EMA are usually seen while TTF-1 and mono CEA staining was negative (Figure 1b). Immunohistochemical examination was performed for differential diagnosis of the tumoral foci. Cytoplasmic staining with CK 7, CK 5/6 and calretinin and membranous staining with HBME-1 and EMA are usually seen while TTF-1 and mono CEA staining was negative (Figure 1b).

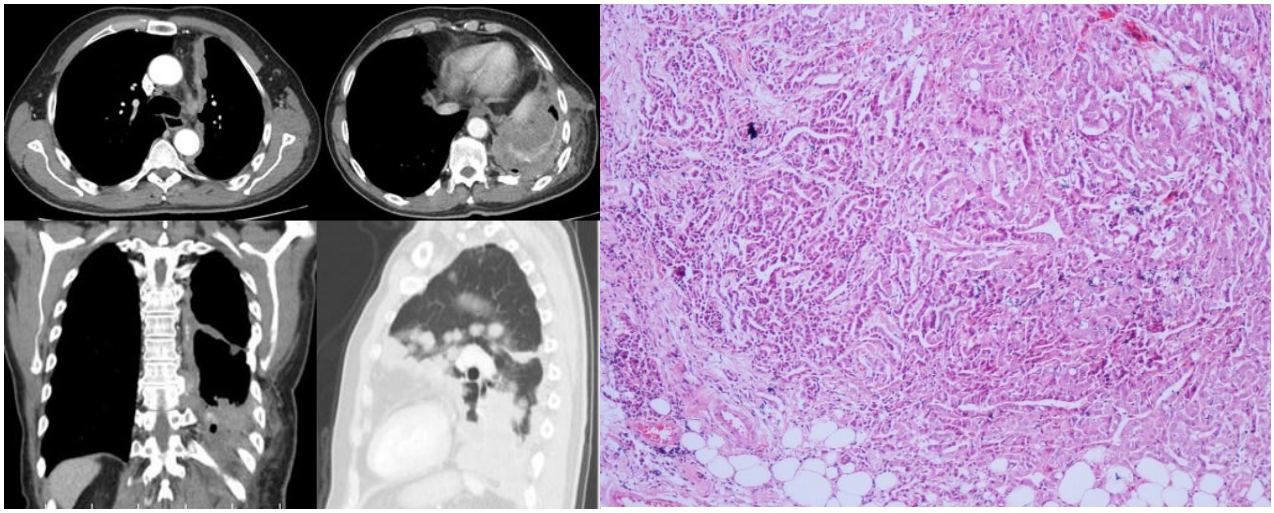

Figure 1a: Thoracic Computed Tomography of a patient diagnosed with malignant mesothelioma. Volume loss of left lung, nodular pleural thickness, pleural effusion and basal posteromedial calcified plaques are observed. Left chest wall invasion is also viewed. **1b:** Same patients biopsy specimens microscopic view.

Thorax CT of 16 patients diagnosed with pleuritis showed pleural effusion in 11 cases (mostly unilateral); pleural thickening in 15 patients (mainly nodular), mediastinal pleural thickening in six patients, interlobar fissure thickening in 13 patients and lung volume reduction in 10 patients (Figure 2a). Pathologically spindle-shaped fibroblasts with vesicles contain large nuclei with prominent pathologic nucleoli and an abundant eosinophilic cytoplasm on the fibrous tissue, and fibrin deposits were revealed. Immuno-histochemical examination showed cytoplasmic staining with calretinin and negative for HBME-1. (Figure 2b)

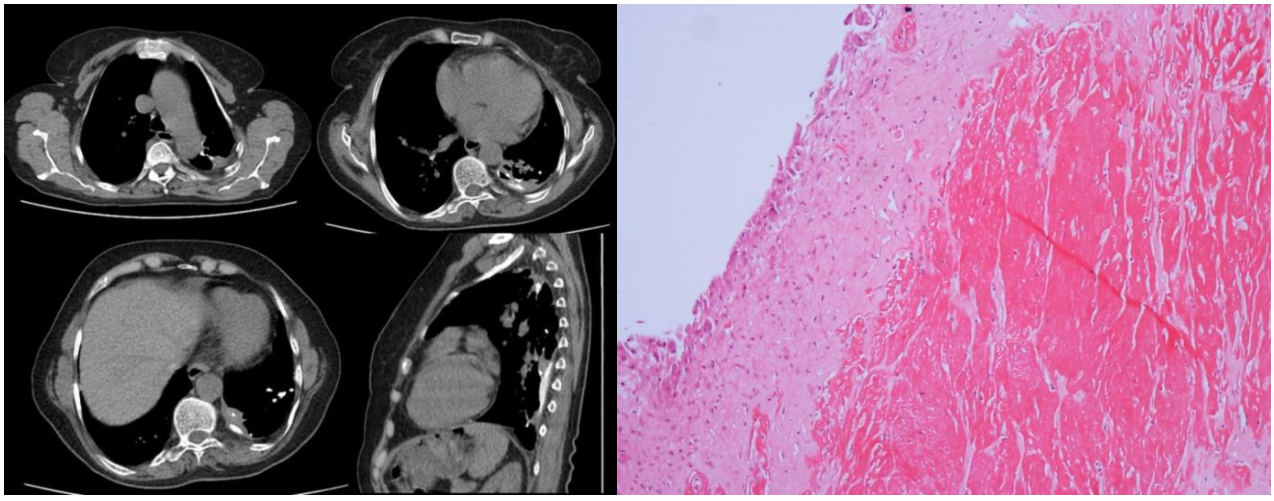

Figure 2a Thoracic Computed Tomography of a patient diagnosed with fibrinous pleuritis. Volume loss of left lung, left sided nodular pleural thickness, pleural plaques, and left chest wall invasion are observed. **2b:** Histopathological assessment of the same patient.

Thoracic CT of six patients diagnosed with chronic granulomatous inflammation showed pleural effusion in four cases, pleural thickening in six patients (mainly nodular), mediastinal pleural thickening in two patients, interlobar fissure thickening in five patients, and lung volume reduction in four patients (Figure 3a). Calcified granulomatous inflammation was present in four of these patients and were found to be compatible with tuberculosis. Calcification necrosis was not detected for the other two patients. Pathologically, epithelioid histiocytes communities around necrotic material, giant cells that nucleus settled in the periphery and lymphocytic infiltration were viewed Figure 3b.

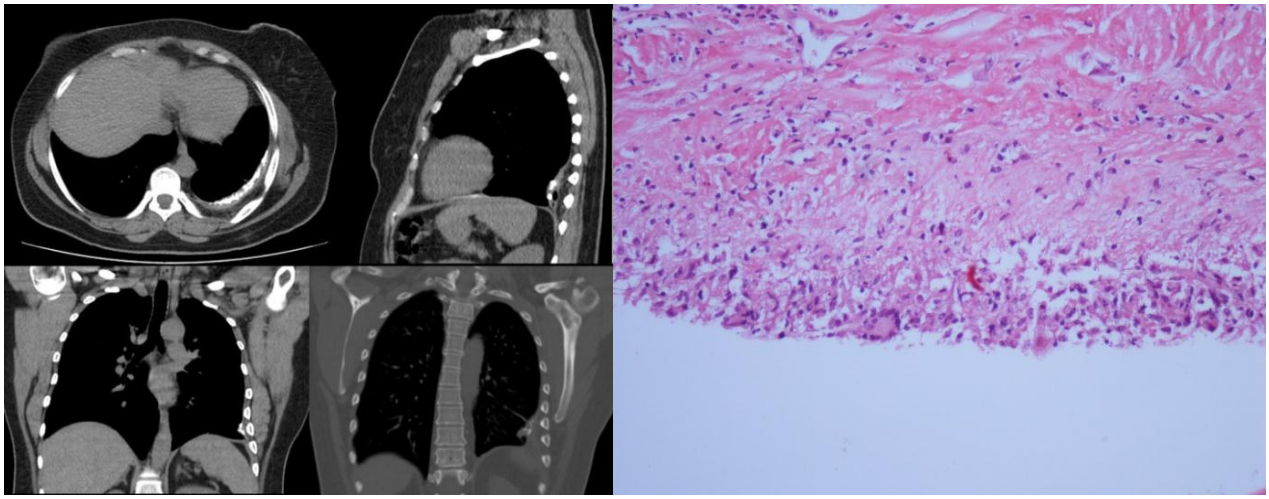

Figure 3a: Thoracic Computed Tomography showed pleural thickness of left basal lung and pleural calcification in a patient diagnosed with chronic granulomatous inflammation. **3b:** Histopathological assessment of the same patient

Thoracic CT of six patients diagnosed with malignant epithelial tumor metastasis showed pleural effusion in four patients (usually unilateral), pleural thickening in six patients (mainly nodular), mediastinal pleural thickening in two patients, interlobar fissure thickening in five patients and lung volume reduction in four patients (Figure 4a). Additionally, there were metastatic masses in the lung parenchyma in two patients. Pathological examination revealed minor adenoid structures and infiltrative foci formed by atypical epithelial cells with large hyperchromatic nuclei and distinct pleomorphism. Immunohistochemical staining were positive for HBME-1,pan CK, CK7, EPCAM, mono CEA, TTF-1 and calretinin while D2-40, Desmine, P63, P53, CDX2 and B72.3 were negative.

Thoracic CT of a 70 years old man showed irregular pleural thickening reaching 12 mm in thickest half. There were no pleural effusion or pleural calcification. Pathological examination suggested reactive mesothelial cells with the nuclei containing vesicles and abundant eosinophilic cytoplasm in the vicinity of the fat tissue and many lymphocytes in dispersed settlements. Immuno-histochemical staining showed positive staining with LCA, CD20 and CD5.

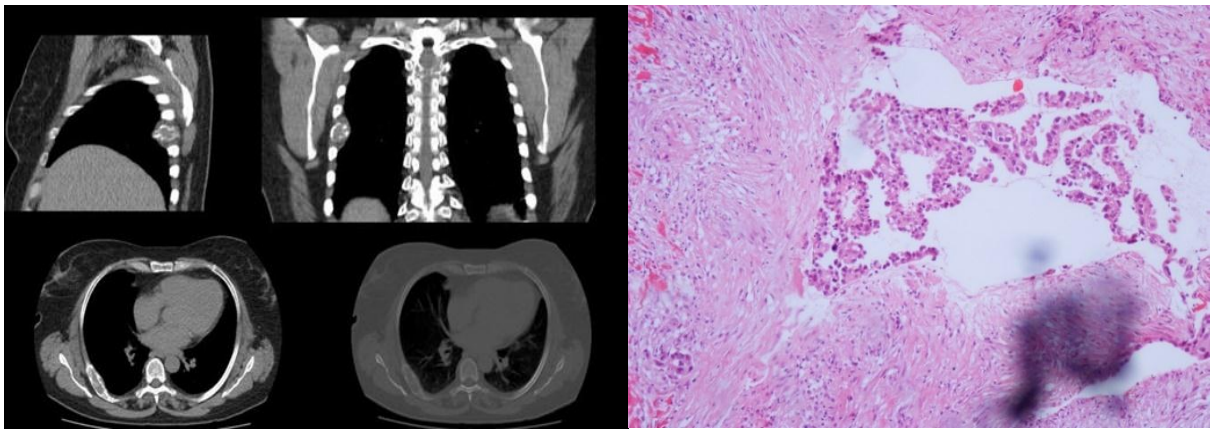

Figure 4a: Thoracic Computed Tomography findings of a patient whose diagnosis is malign epithelial tumor metastasis. A heterogeneous hypodense mass lesion includes soft tissue components on the right posterolateral are clearly seen. This lesion leads to an expansion and destruction of sixth rib. The vicinity of the lesion showed irregular pleural thickening. **4b:** Histopathological assessment of the same patient.

A 55 year old man with a history of asbestos exposure and suspected of mesothelioma was diagnosed with localized fibrous tumor. Thoracic CT of this case showed lobulated contoured pleural effusion trending right major fissure and surrounding lung parenchyma. The other tomography findings indicated linearly calcified plaque in the right lung basal and local nodular-irregular thickening of the mediastinal pleura and upper lobe anterior segment. In histopathological examination, proliferated mesothelial cells with stromal infiltration was observed although cellular atypia was not.

In two patients (a 82 years old man and a 68 years old woman) were diagnosed with reactive mesothelial hyperplasia. In tissue sections, pleural inflammation and fibrosis and proliferated mesothelial cells without atypia was observed. In thoracic CT, concentric pleural effusion reaching pleural fissure and local pleural thickening reached a thickness of 14 mm in posterobasal and upper lobe anterior segments of lung were also observed. Linear calcified pleural plaques and volume loss of affected lung were other findings.

DISCUSSION

In the cases with pleural fluid or masses that cannot be diagnosed with repeated thoracentesis or pleural biopsy, thoracoscopy and then thoracotomy are sequentially performed if necessary for definitive diagnosis[1,2]. The most widely used method in the diagnosis of pleural diseases is VATS[1,3]. VATS provides access to all pleural space, and allows biopsy accompanied by direct imaging. Pleural cavity is evaluated in the most appropriate way with video assistance and accompanied monitoring capabilities provide homogeneous and full pleurodesis chances at the top level[1,2]. Less surgical trauma and postoperative pain, preserved lung function, short duration of hospital stay, and better cosmetic results are the advantages of VATS when compared with thoracotomy[1,3]. The significantly low perioperative mortality (0.5%) rates, makes VATS a safe and a well-tolerated procedure[1]. VATS is able to diagnosis pleural diseases with 96% sensitivity and 98% specificity[1,3]. We use VATS commonly and effectively in our clinic, especially for the diagnosis and treatment of pleural diseases. Herein, we present the pleural biopsy results and diagnosis for selected group of patients.

Malignant mesothelioma is a rare primary tumor of the pleura emerging from the serosal surface, and seen in 50% of the asbestos-exposed individuals [4,5]. 14 out of 40 patients in the study had environmental asbestos exposure. The lifetime risk of developing mesothelioma in asbestos workers is 10 % and the latent period of of the disease lasts 25-40 years [4,6.] Unlike the other asbestos related pleural diseases, malignant mesothelioma occurs independent of the dose and leads to symptoms of dyspnea and chest pain[6]. Mesothelioma is histopathologically classified as epithelioid, sarcomatoid, desmoplastic, and biphasic. Epithelioid is the most common subtype[4,5,6]. Mesothelioma may have similar histopathological appearance in cases of reactive mesothelial hyperplasia and neoplastic conditions such as primary lung adenocarcinoma metastasis or other metastatic adenocarcinomas [5,6]. Immunohistochemical staining with HBME 1, calretinin, WT1, CK5/6, D2-40, mono, CEA,

B72.3, ber-ep4, TTF1, MOC-31 and napcine is helpful in differential diagnosis of metastatic tumors while p53, desmine, epithelial membrane antigen, glucose transporter 1 and insulin-like growth factor-II mRNA binding proteine are helpful with differential diagnosis with reactive mesothelial hyperplasia[5,7]. Required immune-histochemical staining was completed for the differential diagnosis of patients for this study group and eight patients are diagnosed with malignant mesothelioma.

Thoracic CT findings of malignant mesothelioma showed irregular thickening of the pleura or parietal nodules, volume loss in the affected hemithorax in varying proportions, ipsilateral pleural effusion, involvement of the mediastinal pleura and the surface of the interlobar fissure with fixation of mediastinum[6,8,9]. The similar findings were also present in our patients. Instead of real tumor calcification, we rather observed calcified pleural plaques embedded in effected pleura.

Although the opposite lung and lymph node metastasis is monitored frequently, mesothelioma penetrates into neighborhood structures such as chest wall, mediastinum, and diaphragm[5,6,9]. Chest wall invasion means extrapleural fatty tissue infiltration and/or direct extension of the tumor into the bone and muscle[6]. If FDG-PET imaging is performed for staging purposes, metastatic spread can be identifiable in approximately 25% of the patients[9]. VATS is the best diagnostic method in malignant mesothelioma. However, when the pleural cavity is filled with tumors, VATS technically, might be insufficient to provide reasonable data and thoracotomy may be required for further investigation[1-3]. None of our patients required thoracotomy for diagnosis.

Although the number of patients suspected of malignant mesothelioma clinically and radiologically was 25 in our study, the number of patients with histopathological diagnosis was 8. When these data are evaluated in our study clinical/radiological diagnostic sensitivity was 100%, specificity was 46.8%, positive predictive value (PPV) was 32% and negative predictive value (NPV) was 100%. We think that the low PPV is depend on there is no specific radiological findings available for mesothelioma.

Reactive pleuritis is a process that can be accompanied by inflammatory cell infiltration[10]. Fibrinous pleuritis is the appearance of exudate in pleural surfaces, organized pleuritis is the appearance of fibrin organization released by granulation tissue and fibrinous pleuritis is appearance of mature connective tissue[5,10]. Lymphocytes, lymphoid aggregates, plasma cells, eosinophils or granulomas can be viewed at different rates in pathological specimen[10]. This fact creates an organized fibrous tissue and pleural plaques. Pleural plaques may be ossified and calcified. Local, nodular or diffuse pleural-based masses observed in radiologically. In such cases, it is hard to distinguish pleuritis from malignancy in both radiologically and macroscopically[5,6,10]. Although the pre-diagnosis was malignancy in mostly of our patients, histopathological diagnosis were mainly pleuritis.

Pleural metastasis can also cause pleural effusion[5,6]. Tomographic findings are pleural thickening without pleural effusion, uniform pleural thickening, localized pleural masses and significant pleural thickening[6]. Localized pleural metastasis is very meaningful in terms of metastasis. Pleural thickening can be seen in both asbestosis and metastasis[4,6]. Nodular pleural thickening is very typical for adenocarcinoma but is monitored rarely. The finding that usually can only be viewed on radiograph is pleural effusion. On CT, thymoma can mimic Malignant pleural mesothelioma (MPM), however, pleural effusion does not typically occur with thymoma, only round or lenticular pleural masses can be viewed[6]. Calretinin, WT1, D2-40 and cytokeratin (CK) 5/6 are useful immunohistochemical markers for the diagnosis of MPM, as TTF-1 and CEA are markers that typically are positive in pulmonary adenocarcinoma and negative in mesothelioma. The radiological examination of our metastatic group of patients showed nodular pleural thickening and pleural effusion. Primary tumors of patients in this group was breast cancer in two patients, lung cancer in three patients and mediastinal masses in one patient.

Localized Fibrous Tumor (LFT) of the pleura is a tumor arising from the visceral pleura and observed very rarely[5,6,11]. Although it is named as benign mesothelioma in the past, now it is well known that this tumor is originated from submesothelial mesenchymal tissue[5]. It is differentiated from malignant mesothelioma with the lack of exposure to asbestos, have a good prognosis and different treatment modalities[6]. Approximately 30% of LFTs are malignant. It is less than 5% of all pleural tumors and seen in all age groups, makes a peak in sixth and seventh decades[5,6]. LFT is usually discovered incidentally on radiography[6]. It is presented with insulin-like growth factor type 2 production-induced hypoglycemia, hypertrophic pulmonary osteoarthropathy and chest pain. These symptoms regress after surgery[6,11]. The LFT is often caused by visceral pleura. They are usually

solitary, smooth, sharply demarcated, and with the pleural surface. LFT tends to make a wide angle with the pleural surface unless it is huge[5,6]. When it is seated within fissure, LFT can be confused with fissure liquid. Large feeding arteries and calcification can alsobe viewed in LFT[6,11]. Although our front diagnosis is malignant mezothelioma in one of our patients due to enviromental asbestos exposure, his histo-pathological diagnosis was compatible with LFT.

Chronic granulomatous disease such as tuberculosis can make pleural involvement[5,6,12]. In tuberculosis, pleural involvement can appear as pleural effusion, empyema, pleural thickening and pleural calcification. Parenchymal lesions and lymphadenopathy, often accompanied by pleural involvement[5,6]. In the case of tuberculosis pleural involvement, pleural effusion is watched in early stages of the disease and diffuse pleural thickening, adhesions and pleural calcifications tracked over time. Pleural calcification is frequently monitored in chronic inflammatory situations-induced pleural thickening[6,12,13]. Initial diagnosis was tuberculosis in four patients with pleural effusion and mediastinal lymph nodes, which cannot be stretched after the treatment of pneumonia and histopathological diagnosis was compatible with it.

As we have emphasized in our study, pleural thickening and pleural effusion may develop at the end of various pathological processes such as malignancy, infection and inflammation[1,2,6]. Although CT findings in these pathological processes are characteristic, but not pathognomonic like our study[2,6]. But thoracic CT still is a imaging method that is actively used in determining the right position for pleural biopsy, evaluation and clinical monitoring of response to treatment[6,8]. Because pathologies associated with pleural thickening presents with similar clinical and radiological findings, thoracic CT is not sufficient for the diagnosis and differential diagnosis as highlighted in our study. We believe, histopathologic examination is required for diagnosis[1,2,5]. VATS, in addition to histopathological sampling, is the most preferred and common method that can safely be used in the treatment of pleural pathologies[1,2,3,14].

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