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Computed tomography features in malignant pleural mesothelioma and other commonly seen pleural diseases

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Abstract

Objective: To investigate the computed tomography (CT) features of malignant pleural mesothelioma (MPM) cases, comparing them to those in other malignant and benign pleural diseases. *Materials and methods:* We reviewed the CT findings of 215 patients; 99 with MPM, 39 with metastatic pleural disease (MPD), and 77 with benign pleural disease. The findings were evaluated in univariate and multivariate analysis for differentiation of pleural diseases. *Results:* In patients with MPM, the most common CT features were circumferential lung encasement by multiple nodules (28%); pleural thickening with irregular pleuropulmonary margins (26%); and pleural thickening with superimposed nodules (20%). In the majority (70%) of cases, there was rind-like extension of tumor on the pleural surfaces. In multivariate analysis, the CT findings of 'rind-like pleural involvement, 'mediastinal pleural involvement', and 'pleural thickness more than 1 cm' were independent findings in differentiating MPM from MPD with the sensitivity/specificity values of 70/85, 85/67, and 59/82, respectively. 'Rind-like pleural involvement', 'mediastinal pleural involvement', 'pleural nodularity' and 'pleural thickness more than 1 cm' were independent findings for differentiation of malignant pleural diseases (MPM + MPD) from benign pleural disease with the sensitivity/specificity values of 54/95, 70/83, 38/96, and 47/64, respectively. Invasion of thoracic structures such as pericardium, chest wall, diaphragm, mediastinum, with pleural disease and nodular involvement of fissures, was detected infrequently; however, since these invasions were not seen in benign pleural diseases, it was concluded these invasions, if detected on a CT scan, directly suggested malignancy. *Conclusion:* A patient has extremely high probability of malignant pleural disease if one or more of these CT findings are found and the possibility of MPM is high. These findings may be important for patients in bad state or patients who do not want any invasive biopsy procedures. It is also possible to identify cases with a low probability of malignant disease. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Mesothelioma; Pleura; Computed tomography; Asbestos-related pleural lesions

1. Introduction

Malignant pleural mesothelioma (MPM) is an uncommon neoplasm with a poor prognosis [1,2]. The definitive diagnosis of MPM depends on histopathologic evaluation of biopsy specimens [2,3]. In recent years, computed tomography (CT) of the chest has been used for diagnosing, staging and follow-up examinations of patients with MPM [4–6]. The largest series in which the CT features of mesothelioma were described comprised 84 patients from Turkey [7]. That study and subsequent reports have shown that the CT features of MPM are characteristic but not pathognomonic [7–9]. A variety of benign and malignant diseases may cause pleural abnormalities that resemble

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MPM. The most common causes are metastatic carcinoma, tuberculous pleurisy (TP), empyema, and asbestos-related advanced pleural abnormalities [7,8,10]. The pleural responses to these diseases may manifest radiologically as an effusion, pleural thickening, or calcification [8,10]. The characteristic CT appearances of these pleural diseases have been described [10–12].

In only one study, the value of CT in the differential diagnosis of pleural diseases and the overlap between different benign and malignant diseases was analyzed [8]. The conclusion was that most cases of MPM could not be differentiated from metastatic pleural disease (MPD) by CT scan, and that in the presence of pleural thickening, the most useful features for differentiation of malignancy in pleural diseases was the presence of a pleural rind, pleural nodularity, thickening greater than 1 cm, and mediastinal pleural involvement [8]. However, this study had a limited number of patients. The aim of our study was to investigate the CT features of MPM, and other malignant and benign pleural diseases in a large patient cohort.

2. Methods and materials

2.1. Patients

Between May 1989 and October 1998, 215 patients with malignant or benign pleural disease were included in the study retrospectively. All MPM cases diagnosed in this period were included. All patients presented with either MPD, TP, empyema or asbestos-related advanced benign pleural disease (ARBPD). There were 99 patients with MPM, 39 with MPD, 32 with TP, 26 with empyema and 19 with ARBPD. Among the 39 patients with MPD, 21 had bronchial carcinoma, 2 lymphoma, 6 mammary carcinoma, 9 carcinoma from different extrathoracic sites, and 1 malignant melanoma.

The diagnosis of MPM was based on histopathologic examination of pleural tissue samples, obtained by CT-guided biopsy [13], thoracoscopy or thoracotomy. Only patients with a definite histopathological diagnosis of MPM were included. The diagnosis of MPD was similarly based on histopathologic examination. TP was diagnosed if one of the following criteria were met: positive culture of bacilli; presence of caseous granulomas in pleural biopsy tissue; or radiological and clinical evidence of TP with acid-fast bacilli positive sputum followed by response to antituberculous therapy. Empyema was diagnosed if a microorganism was identified in the pleural effusion or purulent pleural fluid was obtained in the absence of any other cause of pleural effusion. ARBPD was diagnosed if the following criteria were met: documented exposure to asbestos; abnormal pulmonary function test with associated radiographic changes; pleural thickening with or without calcification; and at least 12 months of follow-up without any evidence of malignancy. Patients with pleural plaques were excluded.

2.2. Radiology

All 215 patients had a conventional CT scan of the thorax on a Toshiba TCT 600 scanner with 10 mm thick slices and contrast enhancement. Scans were extended into the abdomen in cases of advanced disease or if lesions were near the diaphragm. In selected cases, a 5 mm slice thickness was chosen to evaluate the fissures or pulmonary parenchyma. All scans were filmed separately using lung and soft tissue window settings with suitable Hounsfield units for each patient.

The pre-treatment CT features were evaluated retrospectively by a panel of two chest physicians and two radiologists who were unaware of the histopathologic diagnosis. They reviewed the scans in consensus. The agreement of three observers was accepted as interobserver agreement.

The pleural lesions were classified into three main groups: thickening, pleural based mass, and pleural effusion. Pleural thickening was divided into three subgroups: smooth, irregular, or nodular. A pleural nodule was defined as 'focal pleural thickening of more than 10 mm but less than 30 mm in length'. A nodule of more than 30 mm was classified as a pleural-based mass. The extent of the thickening was classified as focal if it was limited to a single lobe or the equivalent size of the costal surface (Fig. 6A and Fig. 8). More extensive thickening was classified as diffuse (Fig. 9A). If there was circumferential pleural thickening with mediastinal pleural involvement, it was classified as a pleural rind (Fig. 1). In addition, supplementary radiological features including the involvement of mediastinum, pericardium, interlobar fissures or chest wall, the presence of mediastinal lymphadenopathy, invasion of diaphragm or transdiaphragmatic extension, volume loss of the involved hemithorax, pleural effusion and effusion size, were noted. Both hemithoraxes were evaluated for pulmonary parenchymal abnormalities such as tumoral invasion or fibrosis, presence of calcified pleural plaques, and extrapleural (subpleural) fat tissue.

2.3. Statistics

Statistical analyzes were performed using SPSS statistical software. According to the aim of the study, three groups were formed from patients in accordance with their pleural disease: (1) patients with MPM (99 patients), (2) patients with malignant pleural disease (MPM + MPD; 138 patients), (3) patients with benign pleural disease (TP + empyema + ARBPD; 77 patients).

After establishing and classifying the CT findings according to the patient groups, the frequency of finding was compared with univariate analysis except those findings that were established in malignant pleural disease. In univariate analysis X^2 and 'Fisher's Exact' test were used. A two-sided test was used at 0.05 level of significance. The parameters which had P values $\leqslant 0.05$ in univariate analysis for each patient group were included in the final logistic regression models. The importance of a finding was assessed by the P value of the Wald X^2 statistic, the odds ratio (OR) and its 95% confidence interval (CI).

The parameters which were established as independent findings in multivariate analysis were also analyzed for sensitivity and specificity values in differentiating pleural diseases. Sensitivity and specificity values were calculated with sensitivity (TP/[TP + FN]) and specificity (TN/[TN + FP]). TP means the number of true positive diagnoses, TN means the number of true negative diagnoses, FP means the number of false positive diagnoses, FN means the number of false negative diagnoses.

3. Results

3.1. Radiological findings

The CT findings; effusion, effusion size, extension and configuration of lesions, are listed in Table 1.

Although a pleural effusion was present in most patients with MPM, MPD, TP and in all cases with empyema, it was detected in only 16% of ARBPD cases. Minimal and moderate sized effusion was the rule in benign pleural disease.

In the majority of patients with MPM, the extension of tumor on pleural surface was in the form of a pleural rind (Fig. 1). In patients with MPD, TP, ARBPD or empyema, the extension of tumor on pleural surface was mostly diffuse or focal. A pleural rind was also detected in 9% of patients with TP (Fig. 2). In ARBPD, bilateral disease was seen more often (Fig. 3) and the lesions were mostly focal.

In patients with MPM, the most common configuration of pleural lesion on CT scans were 'multiple nodules circumferentially encasing the entire lung' (Fig. 1), 'pleural thickening with irregular pleuropulmonary margin' (Fig. 4), and 'pleural thickening with superimposed separate nodules' (Fig. 5), respectively. If nodular lesions were present, in 48% of MPM cases, most frequently a nodular presentation was seen on CT scan. Pleural thickening was more than 1 cm in 59% of the cases with MPM.

'Pleural thickening with irregular pleuropulmonary margin', 'pleural effusion only', 'pleural-based soft tissue mass' (Fig. 6), and 'pleural thickening with smooth pleuropulmonary margin' were seen most frequently in MPD cases. Pleural thickening was greater than 1 cm in 17% of the cases with MPD.

In patients with TP, the CT scans showed either pleural thickening with irregular pleuropulmonary margin (Fig. 7) or pleural thickening with smooth pleuropulmonary margin (Fig. 2). Pleural thickening was less than 1 cm in most cases. However, in a few cases the pleural thickening was greater than 1 cm; and if these cases had irregular pleural thickening and pleural rind, the differentiation of malignancy could be more difficult (Fig. 7). However, in our study, the number of cases where all these findings coexisted was only 1 in 32 (3%) of the patients with TP. The CT

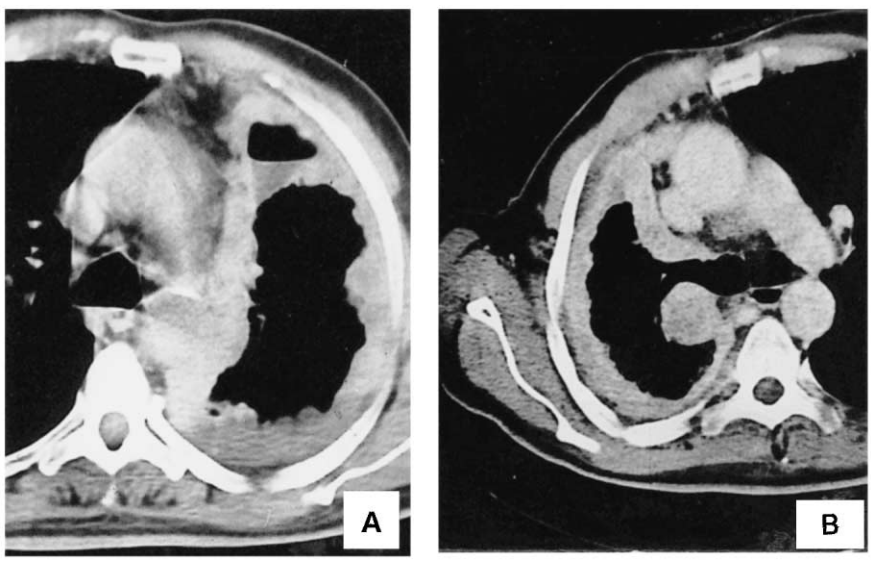

Fig. 1. (A, B) Circumferential pleural thickening with mediastinal pleural involvement in MPM cases (pleural rind).

Table 1
CT findings; effusion size, extension and configurations of lesions

	MPM		MPD		Tuberculous		Empyema		ARBPD	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Effusion	83	84	32	89	30	94	26	100	3	16
Massive	30	30	15	42	5	16	–	–	–	–
Moderate	28	28	12	33	11	34	13	50	–	–
Mild	25	25	5	14	14	44	13	50	3	16
Pleural extension										
Focal	5	5	9	23	5	16	11	42	11	58
Diffuse	20	20	17	44	22	69	15	58	7	37
Rind	69	70	6	15	3	9	–	–	1	5
Pleural thickening +										
Irregular pleuropulmonary margin	26	26	15	39	12	38	6	23	13	68
Smooth pleuropulmonary margin	14	14	6	15	18	56	20	77	3	16
Separate nodules superimposed	20	20	1	3	–	–	–	–	3	16
Multiple nodules circumferentially encasing the entire lung	28	28	4	10	–	–	–	–	–	
Pleural based mass	6	6	6	15	–	–	–	–	–	–
Only pleural effusion	5	5	7	18	2	6	–	–	–	–
Pleural thickening size >1 cm	58	59	7	17	8	25	10	39	10	53

features in patients with the empyema, resembled the findings of the TP cases.

In ARBPD, the configurations of the pleural lesions detected on CT scans were largely pleural thickening with mostly irregular pleuropulmonary margin. However, in 16% of the cases, mimicking separate nodules superimposed on the pleural thickening was detected (Fig. 8). The thickness of the pleural lesions was greater than 1 cm in 53% of the ARBPD cases, while it was largely less than 1 cm in TP and empyema cases.

Involvement of other thoracic structures in the various groups can be seen in Table 2.

Because of contiguous mediastinal pleural involvement, assessment of mediastinal lymphadenopathy and

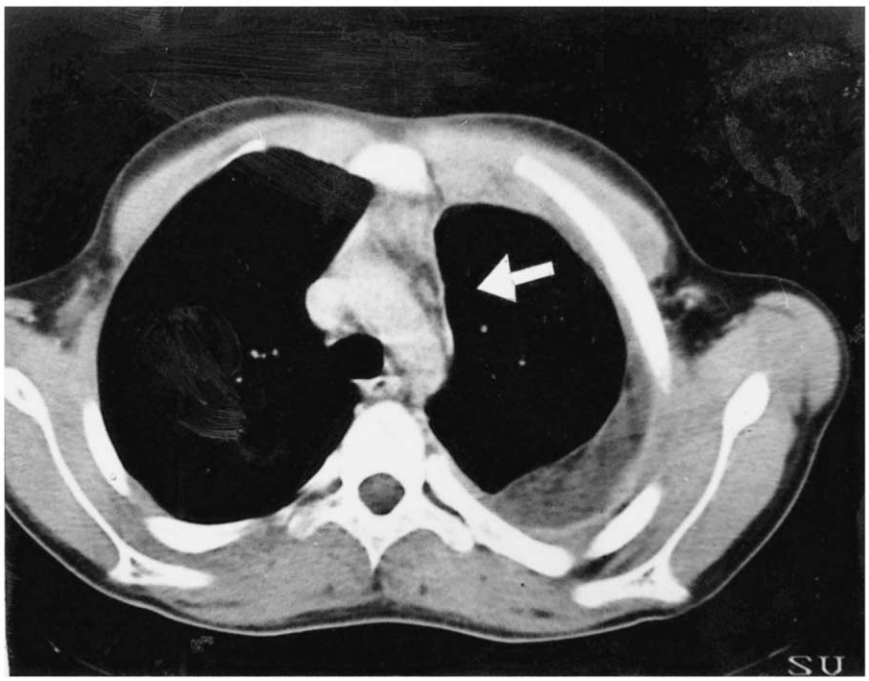

Fig. 2. Circumferential smooth pleural thickening and effusion with mediastinal pleural involvement appearance in a TP case, pleural thickening is less than 1 cm.

mediastinal or pericardial invasion was difficult in patients with MPM (Fig. 1). Involvement of the mediastinum, chest wall, pericardium and diaphragm was only seen in patients with MPM or MPD. Although mediastinal pleural involvement and irregular thickening of the interlobar fissure was seen in all groups, mediastinal pleural involvement was lower in MPD or benign diseases and nodular thickening of the fissure was detected in only malignant pleural disease. Lymphadenopathies (hilar or mediastinal) were seen, with a low detection rate, in all groups except ARBPD.

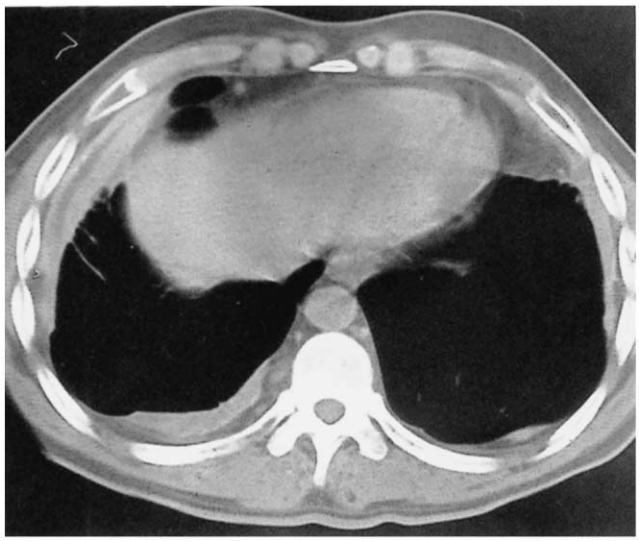

Fig. 3. Bilateral pleural thickening in a case with asbestos-related benign pleural disease.

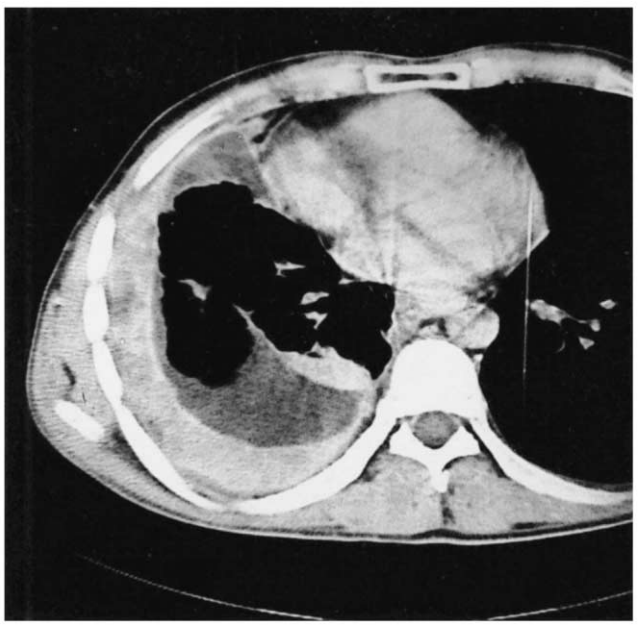

Fig. 4. Irregular pleural thickening in a MPM case, pleural thickening is more than 1 cm.

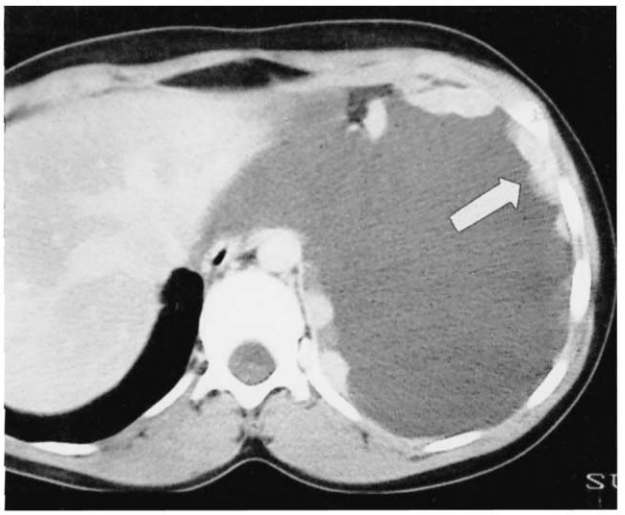

Fig. 5. Pleural effusion and pleural thickening with superimposed separate nodules appearance in a MPM case.

Some findings were important for benign pleural diseases. 'Calcified pleural plaques' were detected in 78% of the cases with ARBPD and were bilateral in most cases, and were seen in only 15% of the MPM cases and in 3% of the MPD cases. 'Parenchymal fibrosis' was seen in 44% of the cases with ARBPD. Increase in the thickness of subpleural fat tissue was found on CT scans of more than half of the patients in almost all benign disease groups; 13 (40%) of TP cases (Fig. 7), 15 (58%) of empyema cases, and 13 (68%) of ARBPD cases (Fig. 9). This feature was seen only in 10% of the cases with malignant pleural disease ($P < 0.001$). In addition, the 'split pleural sign' which suggested 'organisation phase' (Fig. 9B) and 'air bubbles' were seen in empyema cases (Fig. 9B) with a rate of 27 (7/26) and 12 (3/26)%, respectively.

To evaluate the importance of findings for differentiation of MPM and MPD or from benign pleural disease and for differentiation of malignant pleural disease from benign, univariate and multivariate analysis, were used as presented in the methods section. In univariate analysis, all CT findings were tested except those detected only in malignant pleural disease because those findings detected in a CT scan, mostly suggest malignancy. Therefore, the invasions of mediastinal structures, pericardium, chest wall, diaphragm and nodular involvement of fissure were not included in univariate analysis (Table 2).

In univariate analysis the parameters which had P values $\leqslant 0.05$ for each patient group were taken in the final model for multivariate analysis. The results are shown in Table 3.

The parameters assessed as independent findings in multivariate analysis were also analyzed in terms of sensitivity and specificity values in differentiation of pleural diseases. The results are shown in Table 4.

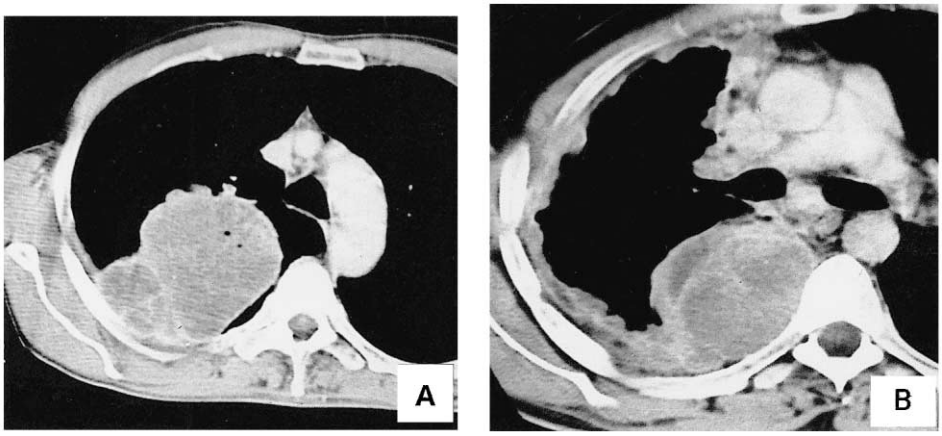

Fig. 6. (A) A soft tissue mass in a MPD case. (B) A soft-tissue mass with circumferentially pleural involvement in a MPM case.

Pleural rind, mediastinal pleural involvement, pleural nodularity and pleural thickening of more than 1 cm each were independent CT findings for differentiation of malignant pleural disease from benign disease with high specificities with the exception of pleural thickening more than 1 cm. Pleural rind, mediastinal pleural involvement and pleural thickening of more than 1 cm had also a moderate importance for differentiation of MPM from MPD.

4. Discussion

Malignant mesothelioma is an unusual tumor with an incidence of 1–2.2/million population [1]. However, in some rural regions of Turkey, malignant mesothelioma is endemic due to environmental exposure to asbestos [1]. Although the clinical features of MPM are well known, a definite diagnosis of this disease depends on extensive histopathological examination of biopsy samples obtained by invasive procedures [3,13].

The radiologic evaluation of MPM was revolutionised with the introduction of CT [14]. CT scans of the chest are now routinely used for diagnosing, staging and follow-up of patients with MPM [4–6,9,14–16]. CT guidance increases the sensitivity of pleural biopsy for MPM and the need for a diagnostic thoracotomy or thoracoscopy is reduced [13,17].

However, it has been suggested that none of the CT findings are pathognomonic for MPM; the pleural response to MPD, TP, empyema, or ARBPD can have similar appearances on CT [7,8,10].

Although the CT findings of common pleural diseases have been described in detail in previous studies [10–12], there is only one study in which the value of CT in differential diagnosis was analyzed [8]. The authors concluded that in most patients with MPM differentiation from MPD by CT scan was not possible. The

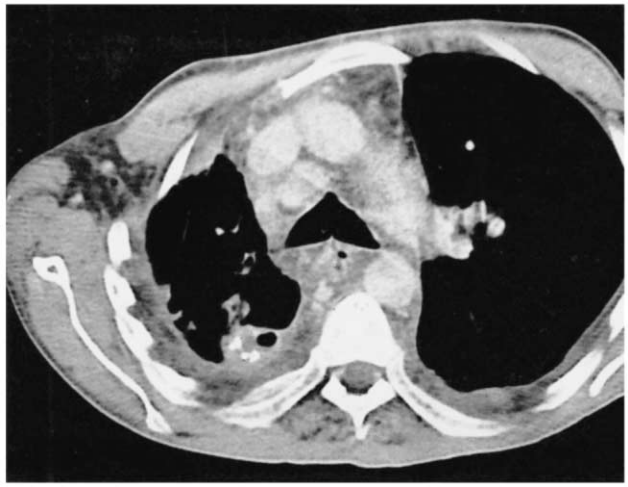

Fig. 7. Irregular pleural thickening with pleural rind appearance in a patient with fibrothorax caused by pleural tuberculosis.

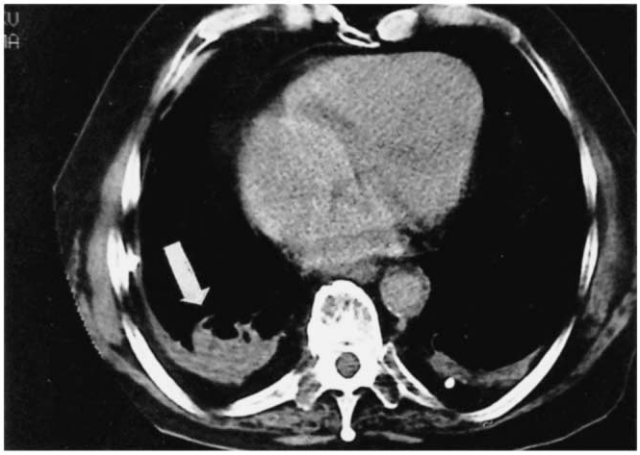

Fig. 8. Pleural lesions mimicking superimposed nodularity in a case with asbestos-related benign pleural disease.

Table 2
Involvement of other thoracic structures

	MPM		MPD		Tuberculous		Empyema		ARBPD	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Mediastinal involvement										
Mediastinal structures	22	22	4	10	–	–	–	–	–	–
Mediastinal pleura[a]	84	85	13	33	7	22	3	12	3	16
Pericardial involvement	25	25	6	15	–	–	–	–	–	–
Chest wall involvement	22	22	2	5	–	–	–	–	–	–
Lymphadenopathy										
Hilar	16	16	10	26	4	13	2	8	–	–
Mediastinal	24	24	20	51	1	3	3	12	–	–
Diaphragmatic invasion	29	29	2	5	–	–	–	–	–	–
Interlobar fissural involvement										
Irregular thickening	19	19	1	3	8	25	5	19	2	11
Nodularity	13	13	1	3	–	–	–	–	–	–
Only effusion	1	1	–	–	4	13	–	–	–	–

[a] Mediastinal pleural involvement includes rind like pleural involvement.

most helpful signs in distinguishing malignant from benign pleural disease were pleural rind, nodular pleural thickening, pleural thickening greater than 1 cm, and mediastinal pleural involvement. It was also reported that pleural calcification usually implies a benign process, and that loss of volume was not a helpful feature [8]. However, this particular study had some limitations, such as patient number and methods. In actuality, it is not known exactly which findings are related to malignant disease and suggestive of tumor type. These findings may be useful in some cases and situations in which a decision for invasive diagnostic procedures is required.

In our study, circumferential pleural involvement (i.e. pleural rind), which has been claimed to be specific for malignant pleural disease in previous studies [8,10], was seen in 70% of MPM cases as compared to only 15% of MPD cases, 9% of TP cases, and 5% of ARBPD cases. It was not detected in empyema. In multivariate analysis, pleural rind was independently assessed for differentiation of MPM from MPD, of MPM from benign pleural disease, and of malignant pleural disease from benign disease.

The most common CT findings in the cases with MPM were multiple nodules circumferentially encasing the entire lung (28%), pleural thickening with irregular

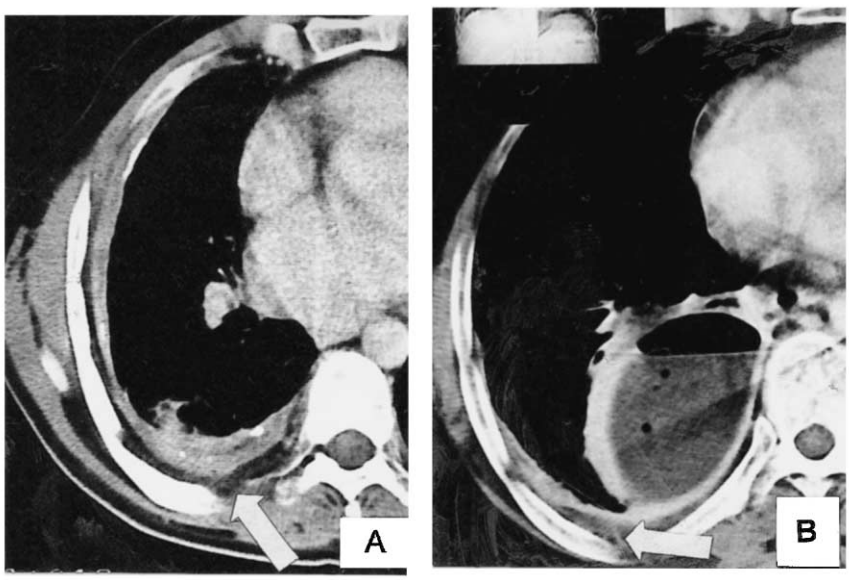

Fig. 9. (A, B) Increased subpleural fat tissue in a case with asbestos-related benign pleural disease and in a case with empyema.

Table 3
The results of multivariate analysis of findings determined in univariate analysis

	Differentiation of MPM from MPD			Differentiation of MPM from benign pleural diseases			Differentiation of malignant pleural diseases from benign		
	OR	CI	*P*	OR	CI	*P*	OR	CI	*P*
Pleural rind	3.17	1.67–6.01	0.0004	21.05	6.75–65.62	0.0000	12.98	4.36–38.67	0.0000
Mediastinal pleural involvement[a]	3.11	1.57–5.98	0.0035	3.53	1.33–9.39	0.01	3.16	1.19–6.14	0.04
Pleural nodularity	1.83	0.91–3.66	NS	14.45	3.58–58.32	0.0002	6.19	1.54–24.97	0.01
Pleural thickness >1 cm	2.17	1.10–4.27	0.03		–[b]		0.40	0.17–0.96	0.04
Irregular fissural thickening	2.41	0.76–7.63	NS		–[b]			–[b]	

OR: Odds ratio; CI: Confidence Interval (95%); NS: Not significant.
[a] Mediastinal pleural involvement includes rind like pleural involvement.
[b] They were not meaningful in univariate analysis.

pleuropulmonary margin (26%), and pleural thickening with superimposed separate nodules (20%). Thus, nodular pleural thickening was seen in 48% of the MPM cases. Nodular pleural thickening was also seen in 13% of MPD. In TP and empyema, the contour of the pleural thickening was characterised by irregular or smooth pleural thickening. Nodular pleural thickening was not seen, however, in 16% of ARBPD cases, pleural thickening mimicking nodularity was seen. Pleural nodularity was independently assessed by CT for differentiation of MPM from benign pleural disease, and of malignant pleural disease from benign, but not of MPM from MPD (Table 3).

Parietal pleural thickening was greater than 1 cm in 59% of MPM cases and in 17% of MPD cases. In 75% of the cases with TP and 61% of empyema cases it was less than 1 cm. On the other hand in slightly more than half of ARBPD cases (53%) the pleural thickening was greater than 1 cm. In multivariate analysis, this finding had importance for differentiation of MPM from MPD, and of malignant pleural disease from benign.

Mediastinal pleural involvement had importance for all groups in terms of differentiation.

Intrathoracic invasion by pleural disease of mediastinal structures or soft tissue, pericardium, chest wall, diaphragmatic involvement, and nodular fissural involvement were only seen in MPM and MPD. Signs of invasion were not a feature of benign disease. We believe that although these findings are uncommon, when seen, their efficiencies are very high in the diagnosis of malignancy. Irregular fissural thickening had importance in univariate analysis, but not in multivariate analysis.

Detection of subpleural soft tissue hypertrophy in fat tissue density was another important supplementary CT finding for benign diseases and was present in half of the benign cases. It is reported that subpleural soft tissue hypertrophy finding is mostly seen in diffuse benign pleural disease and is a reaction to benign inflammation [8,10,11]. The TP case mimicking malignancy in our study had pleural thickening which was greater than 1 cm and had a rind-like irregular pleural thickening (Fig. 7) and had an image of increased subpleural fat tissue. This may be the only finding suggesting benign character of pleural lesion for that case. On the other hand, as well known, although the

Table 4
Sensitivity, specificity, *P* value of CT features obtained by multivariate analysis for the differentiation of the commonly seen pleural diseases

	Differentiation of MPM from MPD		Differentiation of MPM from benign pleural diseases		Differentiation of malignant pleural diseases from benign	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Pleural rind	70	85	70	95	54	95
Nodularity	–	–	48	96	38	96
Pleural thickness >1 cm	59	82	–	–	47	64
Mediastinal pleural involvement[a]	85	67	85	83	70	83

Sensitivity (%); Specificity (%).
[a] Mediastinal pleural involvement includes rind like pleural involvement.

incidence of split sign and air bubble in empyema is low (27 and 12%, respectively), as reported earlier (10), we believe that these findings can be an important CT finding in the diagnosis of empyema since they are not seen in any other disease.

In conclusion, CT can be helpful in differentiating pleural diseases. The definite diagnosis of malignant pleural disease requires a histopathologic evaluation of tissue samples. However, in some cases (such as for patients in bad state or patients who do not want any invasive biopsy procedures) the findings of CT will, for practical purposes, be enough for diagnosis. It is also possible to identify cases with a low probability of malignant disease, where potentially harmful diagnostic procedures could be avoided. As can be seen in Tables 3 and 4, 'pleural rind', 'mediastinal pleural involvement', 'pleural nodularity' and 'pleural thickening of more than 1 cm' each were independent CT findings for differentiation of malignant pleural disease from benign disease with high specificities with the exception of 'pleural thickening more than 1 cm'. When one or more of these CT findings are seen, there is a high probability of malignant pleural disease. The invasion of mediastinal structures, pericardium, chest wall, diaphragm and nodular involvement of fissure, (which were not included in uni- or multivariate analysis due to their direct malignancy suggestion), each can directly suggest a malignant pleural disease. They could not be detected in any patient with benign pleural disease. On the other hand, if a patient has 'rind like pleural involvement' or 'pleural thickness more than 1 cm', then the possibility of having MPM for that patient is rather high.

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