Case Report

Malignant mesothelioma associated with chronic empyema with elevation of serum CYFRA19: A case report

Yukiko Kodama[1], Sakuo Hoshi[2,*], Manabu Minami[3], Masahiro Kiso[4], Tomoko Takezawa[1], Takahiko Arai[1], Yasuo To[1], Shinichi Teshima[4], Naoto Suzuki[1]

[1] *Department of Allergy and Respiratory Medicine, Doai Memorial Hospital, Tokyo, Japan;*
[2] *Department of Respiratory Medicine, The University of Tokyo Hospital, Tokyo, Japan;*
[3] *Department of Radiology, University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan;*
[4] *Department of Pathology, Doai Memorial Hospital, Tokyo, Japan.*

Summary **Malignant neoplasms are reported to occur with long-standing tuberculous pleuritis or chronic empyema. During the clinical course of chronic empyema, subjective symptoms such as chest pain and deterioration of dyspnea and abnormal clinical signs such as increased abnormal chest shadows have frequently been found. Though difficult, differentiating the occurrence of malignant tumors from worsening chronic inflammation is crucial. We report here a case of malignant mesothelioma associated with chronic empyema with elevation of serum CYFRA19.**

Keywords: Malignant mesothelioma, Chronic empyema, CYFRA19

1. Introduction

The main cause of pleural mesothelioma is exposure to asbestos (*1*). However, malignant pleural tumors can also arise in scars from old tuberculosis, especially after therapeutic pneumothorax, and in chronic empyemas and fistulas (*2,3*). Despite repeated biopsies, detection of malignancy near the empyema cavity is difficult in some cases. Histologically, these tumors are reported to differ somewhat from other mesotheliomas (*4*). Reported here is a case of mesothelioma secondary to asymptomatic chronic empyema with elevation of serum CYFRA19.

2. Case report

An 83-year-old man visited this hospital in February 2006 because a civic health examination indicated an abnormal shadow on a chest X-ray of his left lung. The individual had suffered from tuberculous pleuritis in his 20s. He had also been diagnosed with chronic empyema by another hospital one year prior to this visit. Aspiration cytology from the lower left part of the empyema using a 16 gauge needle revealed no malignancy (data not shown). Chest X-rays revealed an opacity with lobulations in the lower left lung and thickening of the pleura. There were calcified lines (arrowheads) in the basal parts of both lungs (Figure 1a). A chest CT scan revealed a large empyema in the lower left thoracic cavity and calcified pleural thickening bilaterally. Irregular pleural thickening was also found along the left thoracic cage (Figures 2a and b). The patient was diagnosed with old tuberculous pleuritis and chronic empyema. At that time, he had no complaints and was treated as an outpatient. In November 2006, he complained of chest pain and exertional dyspnea, so he was admitted. He had no history of drinking or smoking and had never been exposed to asbestos.

On physical examination, his height was 172.5 cm and his weight was 78 kg. He was not febrile (36.4°C), his pulse rate was 72 /min, and his blood pressure was 123/57 mmHg. There were no heart murmurs. Respiratory sounds were decreased in the entire left lung field. Laboratory tests showed a decreased hemoglobin level (11.3 g/dL), elevated blood sedimentation rate (112 mm/h) and elevated CRP (5.0 mg/dL), though no leucocytosis (5,600 /μL) was seen. Ventilatory function tests showed a %VC of 51.5% and

Correspondence to: Dr. Sakuo Hoshi, Department of Respiratory Medicine, The University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan;
e-mail: shoshi@mol.u-tokyo.ac.jp

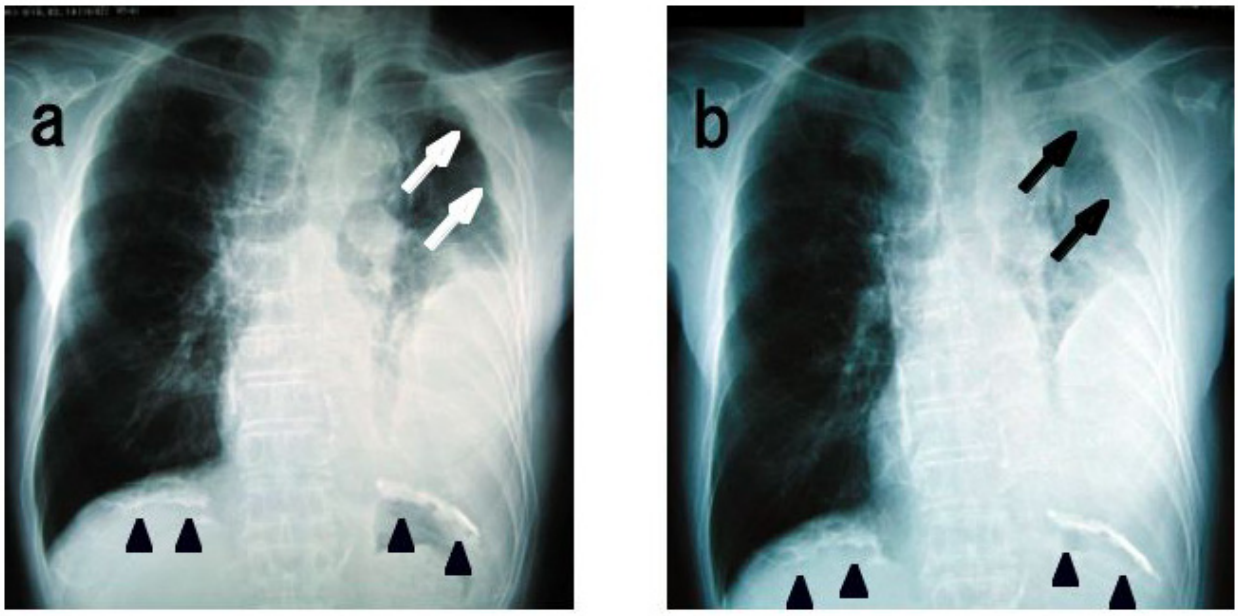

Figure 1. Serial images of chest X-ray. a: A chest X-ray from the first visit shows an opacity with lobulations in the lower left lung and thickened soft tissue density (arrows) along the pleura in the upper lung. There are calcified lines (arrowheads) in the bilateral bases of the lung. *b*: A chest X-ray on admission shows the increased size of the lobulated opacity in the left lung. The upper part of the opacity also has increased thickness along the pleura (arrows) with progressively increasing density in the aerated left lung. Calcified lines (arrowheads) in the bilateral bases of the lung showed no change.

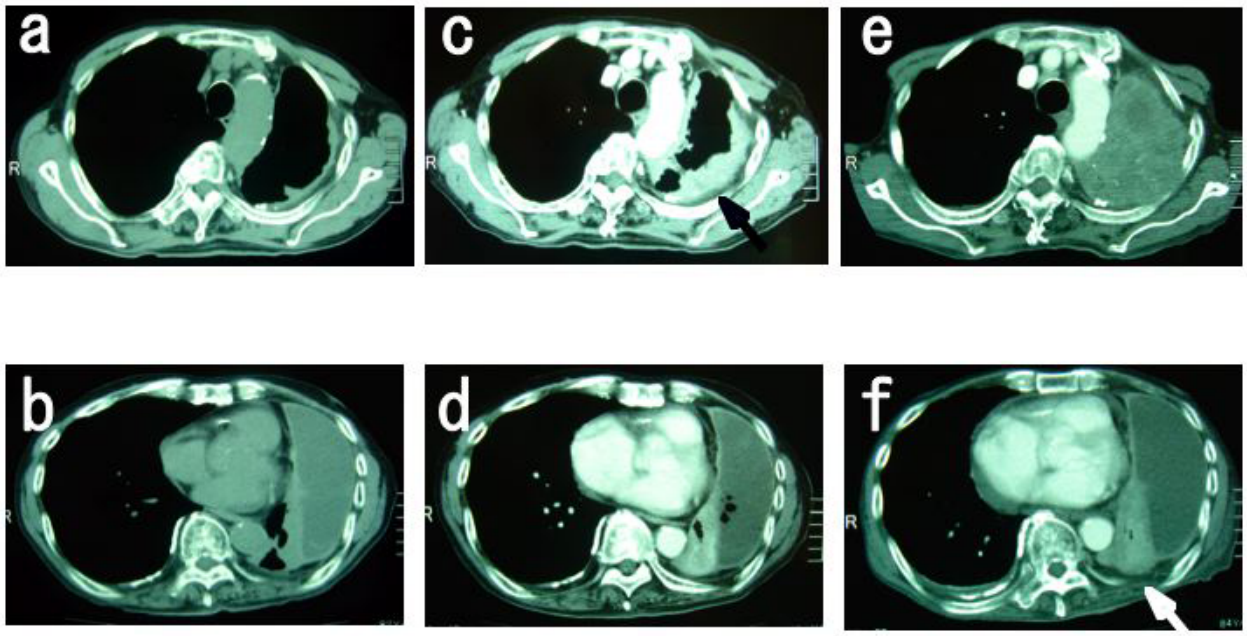

Figure 2. Serial images of chest CT scans. *a* and *b*: Non-contrast chest CT scans on the first visit show pleural thickening along the thoracic cage of the upper left lung with no involvement of the mediastinal side. A large empyema is seen in the lower left thoracic cavity with partial atelectasis of the lower lobe. Some calcifications are observed in the thickened pleura bilaterally. *c* and *d*: Contrast-enhanced CT scans on admission show increased irregular thickening of almost the entire circumference of the pleura involving both parietal and mediastinal sides. The increased size of nodular thickening along the dorsal part (arrow) is 1 cm greater than that in the chest CT scan from the initial visit. The empyema in the left thoracic cavity shows air bubbles probably due to the effect of aspiration cytology. *e* and *f*: Contrast-enhanced CT scans just before death show a fully consolidated upper lung. The size of the empyema is generally consistent but progressive nodular bulging is seen (arrow) in the lower left lung.

a $FEV_{1.0\%}$ of 67.5%. Arterial blood gases (at room air) were as follows: pH 7.45, $PaCO_2$ 41.4 mmHg, PaO_2 90.3 mmHg, O_2 saturation 97.2%. Tumor markers were normal (CEA was less than 0.5 ng/mL, CA15-3 was 5.8 U/mL, CA125 was 32.2 U/mL and NSE was 6 ng/mL). A chest X-ray revealed a diffuse, increased opacity in the entire left lung and thickening of the chest wall over it, indicating deterioration from the chest X-ray during the initial visit (arrows). Calcified lines in the basal parts of both lungs showed no change (arrowheads) (Figure 1b). A contrast-enhanced chest CT scan showed no remarkable change in the chronic empyema in the lower left thoracic cavity but increased irregular thickening of almost the entire circumference of the

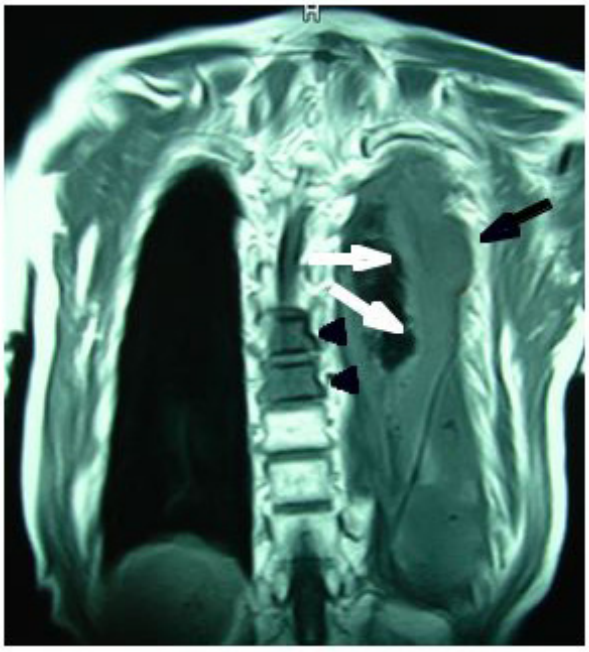

Figure 3. Coronal T1-weighted MR images on admission (SE 500/10) revealed chronic empyema in the lower left thoracic cavity. The irregular mass extends along the pleura and the medial wall of the empyema (arrows). The aerated lung partially is atelectatic with decreased volume. Two thoracic spines (arrowheads) appear as hypointense, suggesting metastasis.

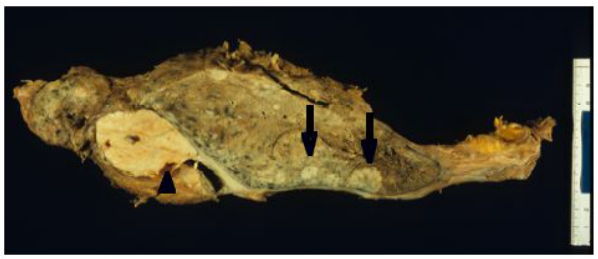

Figure 4. The left lung specimen shows irregular thickening throughout the pleura. Several tumor nodules were seen along with invasion of the lung (arrows). The pleural tumors tightly adhered to the thoracic wall (arrowhead).

pleura (Figures 2c and d). Coronal MR T1-weighted images revealed chronic empyema in the lower left lung and a consolidated mass surrounded by a low-intensity rim (arrows) in the upper left lung (Figure 3).

Aspiration cytology from the soft tissue density lesion along the lower left part of the empyema using a 16 gauge needle again revealed no malignancy (data not shown). CT-guided needle biopsies of the upper thickening pleura were then performed using an 18 gauge core biopsy needle. Pathological examination revealed an epithelial mesothelioma. Immunostaining was positive for anti-calretinin. Immunostaining was also positive for anti-keratin, weakly positive for anti-vimentin, anti-D2-40, and anti-EMA, but negative for anti-CEA (data not shown). Though he was 83 years old, the patient's performance status was good (PS1), and he and his family were eager for treatment, so combination chemotherapy of cisplatin (60 mg/m^2, day 1)/ gemcitabine (80 mg/m^2, day 1, day 8) was given. Chemotherapy was stopped, however, during the second course on account of a high fever. The masses were slightly reduced in size (data not shown). The patient was followed with best supportive care. Chest X-rays while the patient was an outpatient gradually showed deterioration and gradually elevation of the serum level of CYFRA19 (11.5 ng/mL in July 2007 and 59.2 ng/mL in January 2008) while the serum level of CEA remained within the normal range. In February 2008, a contrast-enhanced chest CT scan showed similar findings of chronic empyema in the lower left thoracic cavity as well as a fully consolidated upper left lung (Figures 2e and f). The patient died of mesothelioma in April 2008. Autopsy showed pleural thickening throughout the pleura. Several tumor nodules were seen along the pleura with invasion of the lung (arrows).

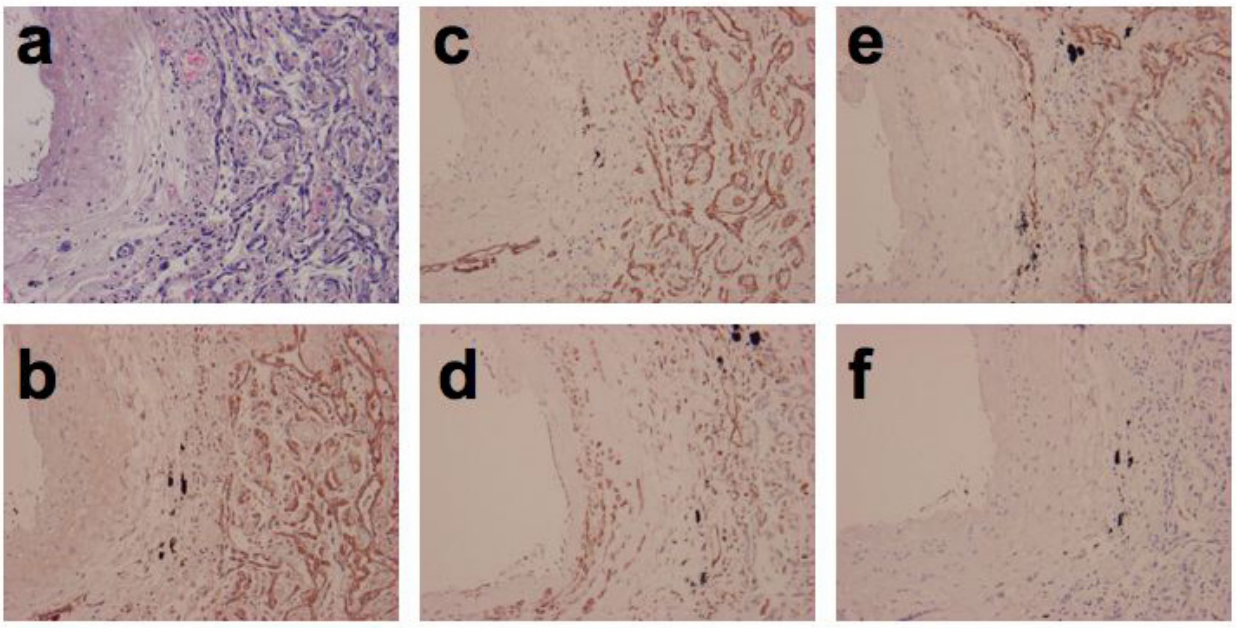

Figure 5. An autopsy specimen of the pleural tumor in the left thoracic cavity shows a pleomorphic tumor (hematoxylin-eosin) that was (*a*) positive for calretinin (*b*), keratin (*c*), vimentin (*d*) and D2-40 (*e*) staining. CEA staining was negative (*f*) (×100).

The pleural tumors tightly adhered to the thoracic wall (Figure 4). Tumor invasion and plaque were seen in the left diaphragm. A massive tumor was noted on the lower surface. Metastatic tumors were seen in the hilar lymph nodes, mediastinal lymph nodes, right lung, stomach, liver, kidneys, spine, and Douglas fossa. Cancerous peritonitis was also seen (data not shown). Autopsy specimens from the pleural cavity of the left lung showed a pleomorphic tumor that was positive for calretinin, keratin, vimentin, and D2-40 and negative for CEA, consistent with malignant mesothelioma (Figure 5). Fibrin and neutrophils were also seen in the autopsy specimen from the pleural cavity of the lower left lung, consistent with chronic empyema, but tuberculosis was not specified as the cause (data not shown).

3. Discussion

Reported here is a case of malignant mesothelioma associated with chronic empyema secondary to tuberculous pleuritis with elevation of serum CYFRA19. The patient had never been exposed to asbestos, and autopsy specimens showed no asbestos bodies, either. Malignant mesothelioma is reported to arise even without exposure to asbestos. Etiologic factors of non-asbestos-related malignant mesothelioma include serious lung diseases, tuberculosis, chemical pneumonia, radiation, and industrial dust and chemicals other than asbestos. A chronic inflammatory process is also suggested as a causative factor, and peritoneal malignant mesothelioma is reported to arise from recurrent peritonitis (*5-7*). The main latency time is reported to be 16 years from the first pneumothorax treatment or signs of empyema to the appearance of symptoms from the tumor (*4*). In this case, the patient was diagnosed with chronic empyema one year before his visit, but his clinical history suggested that he might have suffered from tuberculosis in his 20s. Thus, the latency time in this case may be over 60 years. The mechanism by which mesothelioma occurs due to chronic inflammation is not clear, but involvement of pleural damage and repair is suggested, and persistent inflammation is thought to be required as a factor for malignant mesothelioma (*1*). The Epstein-Barr virus may be implicated in pyothorax-associated lymphoma though not in mesothelioma (*8*).

A differential diagnosis based on malignant pleural disease is extremely difficult in a patient with chronic empyema because malignant mesothelioma has no specific symptoms (*4*). However, deterioration of dyspnea, chest pain, fatigue, and fever are suspected of indicating a malignant disease since these symptoms are uncommon in chronic empyema. In the current case, the patient complained of chest pain and exertional dyspnea on admission. Serum CYFRA19 may have some diagnostic significance. A case of malignant pleural mesothelioma with elevation of CYFRA19 has been reported (*9*). An elevated CYFRA21-1 level with a low CEA level in pleural effusion is also reported to strongly suggest mesothelioma (*10*). In the current case, the serum level of CYFRA19 gradually rose while the serum level of CEA remained negative during the clinical course. Thus, the serum levels of CYFRA19 and CEA may have diagnostic value.

Chest CT scan features suggestive of a malignant pleural disease are reported to be: a pleural rind (specificity 94%, sensitivity 41%), nodular pleural thickening (specificity 94%, sensitivity 51%), parietal pleural thickening greater than 1 cm (specificity 94%, sensitivity 54%), and mediastinal pleural involvement (specificity 88%, sensitivity 56%). On the other hand, a feature suggestive of a benign disease is pleural calcification (specificity 46%, specificity 92%) (*11*). Enhanced chest CT scans reveal "the split pleural sign" and curvilinear enhancement as inflammatory hyperemia of the separated visceral and parietal pleura (*12,13*). On both MR T1-weighted and T2-weighted images, chronic empyema itself is clearly separated by low-intensity rims and shows signal intensities different from those of the tumor (*2*), which coincides with findings in the current case. In a study of radiological evaluation, empyema also displays malignant features, so one or more these findings suggest a high probability of malignant pleural disease (*14*).

Final diagnosis depends on biopsy results, but aspiration biopsies with thin needles are generally useless. Aggressive needle biopsies with large-bore needles or, if possible, incisional biopsies at surgery are recommended (*2*). The diagnosis of malignant mesothelioma is reached by cytology (accuracy 25-30%), blind pleural biopsy (accuracy less than 30%), and CT-guided pleural biopsy (accuracy 85%). Thoracoscopy-guided pleural biopsy (accuracy 98%) can be helpful but invasive, so a CT scan should be performed to reach a diagnosis (*15*). In the current case, the CT findings of a pleural rind and mediastinal pleural involvement on the first visit suggested a malignant disease, but the two aspiration biopsies of the lower chronic empyema revealed no malignancy (data not shown) while needle biopsy of the upper pleural thickening did (data not shown). Malignant tumors associated with chronic empyema are reported to originate in the chest wall around a chronic empyema, and chiefly along the parietal pleura of the empyema (*2*), which coincides with findings in the current case. Thus, this case also suggests the necessity for aggressive needle biopsies and that the biopsy portion of centesis should be carefully decided.

The median survival of patients with malignant mesothelioma from the time of diagnosis is 12 months. Chemotherapy with cisplatin plus gemcitabine results in response rates of 48% and a median survival of 13 months, which represents a significantly longer survival

and better quality of life than with best supportive care (*1,15*). Early chemotherapy is more effective than delayed chemotherapy in symptomatically stable patients. However, there are limited indications for chemotherapy in terms of performance state and age (*16,17*). The current patient survived 16 months from the time of his diagnosis, which was 3 months longer than the median survival in months. Chemotherapy with cisplatin plus gemcitabine might have contributed to his survival, though it was stopped after the first course.

In conclusion, chronic empyema can induce malignant mesothelioma over a long clinical course. CT scans are recommended even in asymptomatic patients with chronic empyema at least every year. The elevated serum level of CYFRA19 and the normal serum level of CEA may also have diagnostic value. Particularly in the case of CT findings suggestive of malignant disease, physicians should not hesitate to perform more invasive examinations such as a core needle biopsy to make a diagnosis.

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