



## Case report

## A 75 year old male with recurrent unilateral pleural effusion and positive ANA

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## A B S T R A C T

This case report describes the clinical course and diagnostic challenges arising in a 75 year old man who initially presented with progressive shortness of breath. Imaging revealed a pleural effusion, which was recurrent following thoracentesis. While his initial workup suggested an autoimmune etiology, further diagnostic testing revealed a diagnosis of malignant pleural mesothelioma. Curiously, the patient had no known asbestos exposure, which is classically associated with acquired mesothelioma. There are a small number of similar cases with a possible overlap between positive autoimmune serologies and mesothelioma; however, the underlying pathophysiology remains elusive. It is the authors' goal to contribute this case to the few cases describing such overlap syndromes.

## 1. Case presentation

A 75-year-old lifelong non-smoking Caucasian man presented to clinic with progressive debilitating dyspnea with minimal cough for the last several months. He works as a contractor with no known asbestos, silica, or other environmental exposures.

Physical exam revealed a well-built and nourished male who was hemodynamically stable with decreased breath sounds throughout the right hemithorax. A chest roentgenogram done on the day of his clinic visit revealed a large right-sided pleural effusion and hence he underwent an ultrasound-guided thoracentesis with removal of 3 L of serosanguineous pleural fluid. The analysis from the pleural fluid revealed the following: 190,000 RBC/uL, 542 total nucleated cells/uL (17% neutrophils, 25% lymphocytes, 54% macrophages, 3% eosinophils, 1% basophils), total protein 5.7 g/dL, LDH 366 u/L. On further analysis of the pleural fluid it was revealed to be exudative in nature and macrophage predominant. The Gram stain, culture and cytology were negative. Lab work done on the same day as his clinic visit also revealed an elevated ESR (52mm/hr), CRP (32.7mg/L), a positive ANA (enzyme-linked immunoassay, no titer obtained), double-stranded DNA (15 IU/ml) and rheumatoid factor (16 IU/ml), though he denied any symptoms suggestive of a rash, oral ulcers, joint pains or joint swelling or morning stiffness. A rheumatology consultation was obtained. Given the positive serology markers, the effusion was thought to be related to connective tissue disease and hence he was started on empiric prednisone therapy.

Despite the thoracentesis and prednisone, he continued to have debilitating dyspnea. On follow-up within a week, thoracic ultrasound

revealed reaccumulation of the pleural fluid. Repeat fluid analysis revealed red, turbid pleural fluid. The repeat analysis showed 80,000 RBC/uL, 881 total nucleated cells/uL (9% neutrophils, 57% lymphocytes, 1% monocytes, 26% macrophages, 5% eosinophils, 1% basophils, and 1% mesothelial cells). Cultures were sterile and cytology was negative for malignant cells.

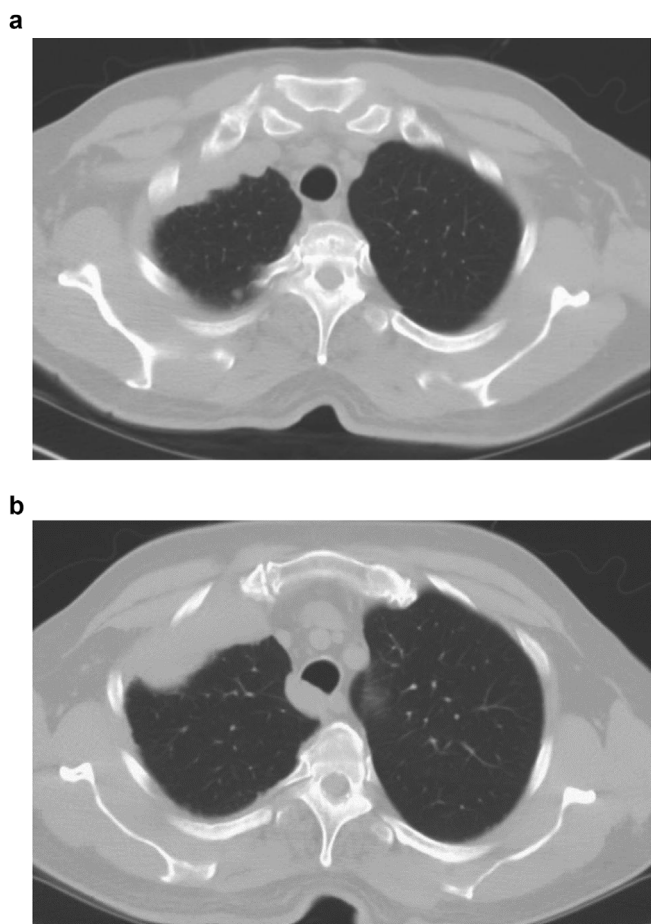
A CT scan of the chest was obtained which showed the presence of multiple pleural masses and nodules involving the right hemithorax with large lobulated pleural thickening of the anterior right upper lobe along with nodularity of the right mediastinal and right diaphragmatic pleura (Fig. 1a and b).

A medical thoracoscopy was performed which revealed plaque-like tumor on the parietal pleura with islands of exophytic lesions in between (Fig. 2). Parietal pleural biopsies revealed the presence of epithelioid subtype of mesothelioma.

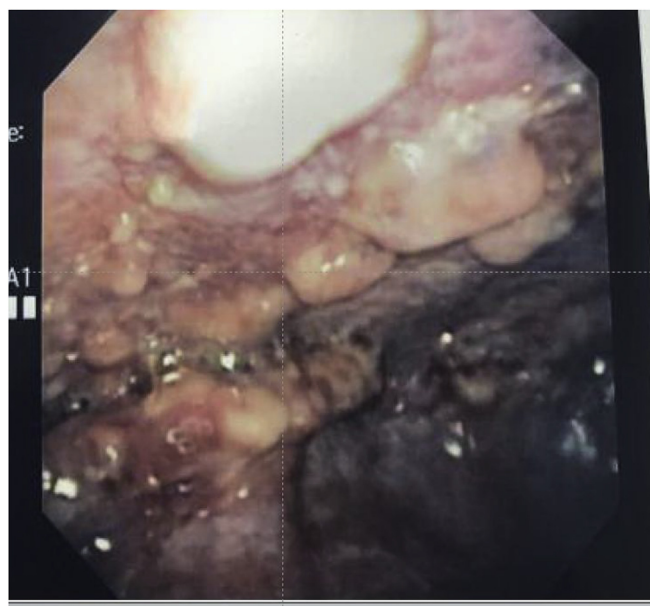
A subsequent PET scan done revealed the presence of hypermetabolic pleural-based masses of the right hemithorax with bilateral hypermetabolic and mediastinal lymph nodes. This was followed by endobronchial ultrasound-guided transbronchial needle aspirates off the lymph nodes bilaterally which revealed the presence of reactive bronchial cells and lymphocytes but no malignant cells at any of the lymph nodes stations.

He was seen by an oncologist and given the involvement of the fissure he was deemed not a candidate for pleurectomy but for a pneumonectomy instead. Since he refused a pneumonectomy, chemotherapy with carboplatin and pemetrexed was initiated.

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**Fig. 1.** a and b: CT scan of the chest revealing right sided pleura-based nodules as well as right upper lobe pleural thickening, nodularity of the right mediastinal and diaphragmatic pleural.



**Fig. 2.** Images obtained from thoracoscopy of the parietal pleural surface, revealing plaque-like tumor with islands of exophytic lesions in between.

## 2. Discussion

This is an interesting case of an elderly gentleman with large volume unilateral pleural effusions, negative asbestos exposure, with positive serology suggestive of systemic lupus erythematosus with no other distinguishing clinical features suggestive of SLE who underwent further evaluation to determine an alternative etiology.

Malignant pleural mesothelioma (MPM) is classically described as an asbestos-associated cancer that has increasing incidence worldwide as a result of increased industrialization. The incidence of MPM in the United States is about 20 cases per million in males and 4 cases per million in females. This accounts to an estimated 3300 new cases of MPM per year [1]. The introduction of asbestos precautions in manufacturing in the late 20th century helped to reduce incidence of asbestos-related MPM. Furthermore, our understanding of the physical and immunological mechanisms behind asbestos-related MPM helped elucidate the relationship. For example, chrysotile fibers (white asbestos) were deemed less carcinogenic than amphibole fibers due to certain physical properties of the fiber and the immune system's reaction to fiber exposure [2].

Despite modern efforts to reduce asbestos exposure, a background rate of MPM incidence remains at around 1–2 cases per million [3]. Considered non-asbestos MPM, this background rate may be in part due to unknown exposures. Other potential causes of non-asbestos related MPM include therapeutic radiation exposure [4], carbon nanotube material [5], and certain genetic predispositions [6], among others.

Aside from careful and thorough history and physical examination, imaging is an early diagnostic tool in the evaluation of patients with suspected MPM. PET in addition to CT may add additional information but has poor sensitivity and may be confused for other pleural diseases [7]. FDG-PET may be a better modality in investigating lymphadenopathy as well as metastatic disease [8]. The pleural biopsy remains the diagnostic gold standard for MPM. In one retrospective study of open pleural biopsy patients, it was found that pleural biopsies had a positive predictive value of 99.7% [9]. In addition, pleural biopsies assisted with imaging (CT/ultrasound) have a sensitivity of 86% and a specificity of 100% [10].

Due to the typical presentation of pleural thickening with pleural effusions, thoracentesis and pleural fluid studies may assist with the diagnosis. However, it is difficult for pathologists to reliably differentiate between MPM and benign reactive mesothelial hyperplasia on cytology alone [11].

Treatment for MPM is largely palliative. Potential chemotherapy including combination pemetrexed/cisplatin may be considered as our patient received. Bevacizumab is a potential immunotherapeutic agent [12]. Surgical options for MPM include pleural tissue debulking in an effort to reduce tumor burden. It has been shown that pleurectomy/decortication of MPM is associated with less mortality than extrapleural pneumonectomy alone [13].

Autoimmune syndromes associated with mesothelioma have been numerous in the literature, including stiff-person syndrome [15], polyneuropathy [16], leukocytoclastic vasculitis [17], among others. There are at least two published cases of SLE-associated pericardial mesothelioma [18,19]. Interestingly, prior asbestos exposure has been linked with systemic autoimmune disease including systemic sclerosis, rheumatoid arthritis, and SLE [14].

We did research into factors shared between patients of non-asbestos MPM and autoimmune disease in the absence of known asbestos exposure and found there are very few unifying characteristics between cases. In certain cases, classical autoimmune antibodies are non-reactive [15] while others are reactive [17]. An interesting aspect of the aforementioned case is the autoimmune serologies suggesting SLE, including positive ANA, positive anti-double stranded DNA antibodies, and positive rheumatoid factor. In addition, the patient had no other signs or symptoms consistent with SLE. Like many of the mentioned cases above, the initial diagnosis for presenting symptoms was not that

of MPM but rather of autoimmune disease [15–17]. This suggests that perhaps the differential diagnosis of autoimmune disease presenting with cardiothoracic complaints should expand to include pleural-based malignancies, even in the absence of known asbestos exposure.

It is well known that pleural-based disease is not uncommon with autoimmune disease such as SLE, RA, mixed connective tissue disease, etc. One possibility is that the connection between non-asbestos MPM and autoimmune disease is due to a paraneoplastic processes. Hypothetically, if the processes were truly paraneoplastic in origin, the syndromes should resolve with treatment of MPM. Given the high mortality of MPM, it is difficult to ascertain the feasibility of this hypothesis. The paucity of these cases also makes generalizations difficult. Until further cases are reported, the link may remain obscured.

### 3. Conclusion

This case is unique and challenging as it highlights the diagnostic challenges faced in a male with no history of prior asbestos exposure. It is important to recognize that the diagnosis of MPM is not forthright since falsely positive serology can act as a deterrent and it is challenging for pathologists to delineate between MPM and benign reactive cells. If the index of suspicion is high then it is pertinent to pursue invasive diagnostic modalities. Non-asbestos MPM has been shown to have clinical and serological overlap with autoimmune disease, but so far there are no consistent patterns unifying the pathology.

### Statement of ethics

Written consent from the subject of this case report could not be obtained, as the patient expired during the publication process of this case report. We respectfully have removed patient identifiers in an effort to respectfully comply with the editor's guidelines. This case was presented as an abstract at a professional poster competition, and the authors obtained permission from the corresponding supervising organization to submit in a case report format in another publication.

### Author contributions

T.W., N.J., and M.K. contributed to writing and preparing the manuscript and accompanying figures. Z.D. contributed to the final version of the manuscript. All authors provided feedback and helped develop the manuscript in its final form.

### Disclosure statement

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