CASE REPORT

Unusual presentation and location pleural malignant mesothelioma

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kumara2@ccf.org**SUMMARY**

Pleural malignant mesothelioma is an uncommon tumour of the thorax. We report two cases: a patient with atypically isolated location of the tumour at the right hilum and a young female patient. The histopathological and radiological features are reviewed with reference to relevant literature.

BACKGROUND

The relatively small number of cases in which the tumour locates in the mediastinum is associated to a pericardial origin. To our knowledge, after extensive literature research, this is the only case in which the tumour clearly relates to the mediastinal pleura. The location and mainly cystic appearance of the tumour on CT in this case led us to consider a complex bronchogenic cyst and malignant mesothelioma in first place. The most common CT findings suggestive of pleural mesothelioma are related to pleural thickening greater than 1 cm and the involvement of the mediastinal pleural surface.¹

Given the unusual presentation, tumour markers have played major role in diagnosis. However, the treatment for pleural mesothelioma is unfortunate, and palliative care is the primary goal.

CASE PRESENTATION**Case 1**

A 64-year-old man with a history of smoking presented to our institution with productive cough. He was previously evaluated at an outside facility and treated with over-the-counter medications a few months before; however, symptoms persisted and he developed associated fevers and chills. The patient worked on a ship in Alaska. His physical examination revealed a well-developed, nourished man with unremarkable physical findings. The pulmonary function test showed a restrictive pattern. The chest radiograph showed a well-defined paramediastinal opacity, enlarging the left hilar shadow below the aortic knob. A thoracic CT was obtained at an outside facility, showing the opacity to be a pleural-based hypodense mass, measuring 23×47 mm with well-circumscribed margins. The mass was located in the hilum, encroaching the PA and abutting the descending aortic arch (figure 1). The considered differential diagnosis for this finding was a complex bronchogenic cyst, necrotic tumour and pleural mesothelioma. The fusion positron emission tomography/CT image demonstrated a fluorodeoxyglucose-avid mediastinal mass.

After an attempted thoroscopic biopsy that resulted non-diagnostic, a CT-guided biopsy

revealed cores of malignant tumour arranged in nests and small sheets, with extensive areas of necrosis; however, there was no clear differentiation towards adenocarcinoma or squamous cell carcinoma. The immunohistochemical stains were positive for calcitonin and cytokeratin 5/6, though negative for TTF-1, napsina, p63 and synaptophysin. Further immunostains revealed positive WT-1 and D2-40 and negative MOC-31, CEA and CD15. This profile was consistent with a diagnosis of malignant pleural mesothelioma, epithelioid type (figure 2).

He was considered a high-risk surgical candidate due to the location, and treatment was initiated to reduce the tumour size with six cycles of Cisplatin-based chemotherapy and Alimata and adjuvant use of 65 Gy radiation therapy. The patient was discharged to travel back to his home country 9 months after diagnosis, in a maintenance dose of Alimata chemotherapy. After a 2 month follow up visit the patient denied any cough, dyspnea, chest pain, or hemoptysis. He gained over 10 pounds reaching the pretreatment weight. Repeat CT of chest showed no pathologically enlarged mediastinal or hilar lymph nodes, but prominent areas of patchy ground glass opacities and consolidation in the left lung.

Case 2

A 35-year-old woman presented to the office with a 2 month history of dry, non-productive cough, daily fever and pleuritic chest pain. Her medical history was unremarkable, she was a non-smoker and had no significant occupational exposure. She also stated an associated 10 pound weight loss since the time of presentation of symptoms. The patient was previously worked up at an outside institution in the past and completed the treatment for presumptive pneumonia, without significant improvement. Physical examination performed in our institution revealed decreased right-sided breath sounds posteriorly progressing up to the mid-lung field with dullness to percussion. A chest radiograph was obtained (figure 2) that showed moderately large right-sided effusion with possible areas of loculation along the superior lateral chest wall and at a basal level. Subsequent CT confirmed a large right pleural effusion with loculation (figure 3).

The analysis of a pleural fluid sample from 1690 cc unfixed orange fluid obtained by thoracentesis was significantly positive for AE1/AE2, WT-1, calretinin, D2-40 and CD68. Tumour markers Ber-EP4, MOC-31, CEA, TTF-1 and p63 were negative. However, owing to the persistent

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Figure 1 A 64-year-old man with a history of asbestos exposure. Axial (A and B) and coronal reformatted (C) images of a chest CT scan, soft tissue and lung window shows an isodense mass located in the left hilum between the left pulmonary artery and the descending aorta, with adjacent small parenchyma atelectasis. Fused positron emission tomography/CT scan showing the hilar mass to be fluorodeoxyglucose-avid.

symptomatology and the suspicious imaging findings, a thoracoscopy with biopsy was performed. The histopathological analysis of the sample revealed parenchymal involvement by malignant epithelioid cells with a tubulopapillary arrangement

invading into the adipose tissue. The malignant cells consistently expressed positive WT-1, patchy CK5/6, calretinin and D2-40, and CK7. Tissue tumour markers were accordingly negative for MOC-31, Ber-ep4, CK20 and TTF-1. These morphological

Figure 2 Histopathological analysis of a CT-guided biopsy of the mediastinal mass. (A) H&E, core biopsy $\times 10$ showing infiltrative atypical epithelioid mesothelial cells. The immunohistochemistry stain (B) positive for calretinin and (C) negative MOC-31.

Figure 3 A 35-year-old woman with cough and fever. Posteroanterior and lateral chest radiograph showing loculated pleural effusion in the right hemithorax.

features and immunostaining pattern supported the diagnosis of malignant mesothelioma, epithelioid type with a tubulopapillary morphology.

A PET/CT scan was obtained, and imaging revealed diffuse hypermetabolic uptake with mild nodularity along the right lung pleura and associated large right-sided pleural effusion with atelectasis (figures 4–6). The left lung was clear with no pulmonary nodules, consolidation or pleural effusion.

DISCUSSION

Mesothelioma is a rare type of cancer that primarily affects the lining of the lungs. Approximately, 2000–3000 cases of mesothelioma cancer are diagnosed each year in the USA.² We present two unusual cases of pleural malignant mesothelioma: the atypical localisation of the tumour as a hilar mass and a young female patient of 35 years without significant medical history, who represents a small minority in age-related incidence.

Asbestos is thought to be the single most important risk factor for the development of mesothelioma.¹ This relationship has been described since 1955,³ and the mean latency period after exposure is 35–40 years.^{1–4} Asbestos fibres have shown to induce direct genotoxicity. Phagocytosed asbestos fibres trigger macrophage activation and generation of reactive oxygen and nitrogen species, leading to tissue injury and recruitment of additional inflammatory cells by the release of cytokines that perpetuate inflammation in response. The amphibolic asbestos fibres are persistently extracted from lung alveoli to the parietal pleura resulting in not only chronic serosal excoriation and irritation but also direct DNA damage on mesothelial cells.⁵

In the Italian population, according to the Italian Institute for Occupational Safety and Health, more than two-thirds of the patients with pleural malignant mesotheliomas collected during the past 20 years had significant exposure to asbestosis, in cases of occupational exposed workers, due to non-occupational asbestos exposure in their relatives, and for those people living around factories using asbestos.⁶ Unlike bronchogenic carcinoma, there is no synergistic interaction between asbestos and cigarette smoke affecting the incidence of mesothelioma.⁷

Further non-asbestos-related associations to malignant mesothelioma have been implicated as cofactors, namely mineral fibres as erionite and irradiation. Less frequently, yet unsettled, thorium dioxide, atomic energy work exposure and viruses such as MC29 avian leukosis virus and polioman virus SV40 have evidenced strong cocarcinogenic association.⁸

According to the National Cancer Institute, pleural mesotheliomas most commonly presents in male patients older than 50 years, with a 5:1 male-to-female ratio. Less than 0.1% of

cases reported between 2004 and 2006 were younger than 54 years.² These tumours classically present with dyspnoea and pleural effusion that leads to chest pain. Other less frequently reported symptoms are chronic fatigue, weight loss and clubbing. However, most cases take 3 months to 2 years to from presentation of symptoms to the time of diagnosis.⁹

Imaging evaluation by chest radiograph is the initial screening examination. Mesotheliomas frequently present as unilateral, plaque-like or nodular pleural thickening.¹ A slight right-sided predominance is observed, possibly because of a larger pleural surface area.¹ Between the relatively small number of cases, in which the tumour locates in the mediastinum, most tumours are associated to a pericardial origin. To our knowledge, after extensive literature research, this is the only case in which the tumour clearly relates to the mediastinal pleura. The location and mainly cystic appearance of the tumour on CT in this case led us to consider a complex bronchogenic cyst and malignant mesothelioma in the first place. The most common CT findings suggestive of pleural mesothelioma are related to pleural thickening greater than 1 cm and involvement of the mediastinal pleural surface.¹ Pleural effusion has been described in up to 74% of the cases.⁹

The analysis of a pleural fluid sample is usually the first step in the diagnosis of pleural mesothelioma. Although the fluids have a tendency to be yellow; this colour is reported only in 20%–30% of cases.⁹ Among the tumour markers with diagnostic significance in the serum and the pleural fluid of malignant effusions, the most important are cytokeratin fragment (CYFRA 21–1), CEA, CA 15–3, CA 15–9, TPA, and hyaluronic acid.¹⁰ Nevertheless, pleural fluid cytology findings are often negative despite repeated sampling (table 1).

Several studies have attempted to define a role for serum markers as screening test or a predictive value for the development of pleural mesothelioma in patients with known exposure to asbestos.

The soluble mesothelin-related protein (SMRP) concentrations have extensively been shown to increase in patients with malignant peritoneal mesothelioma (MPM) compared with patients with benign asbestosis, patients with pleural metastases and lung cancer.¹¹ SMRP has moderate sensibility, but high specificity for screening.¹² There is a newer evidence on the role of SMRP in monitoring that has related successful surgical treatment to lowering levels.¹³

Megakaryocyte Potentiating Factor (MPF), another fraction of the mesothelin precursor protein has a reported sensitivity of 91% and a specificity of 100%, however, most patients in which an ELISA rapid detection test was performed, had advanced-stage MPM.¹²

Figure 4 Axial CT images in soft tissue and lung window shows confluent loculated moderate pleural effusion in the right lung, with right lower lobe atelectasis associated.

Early investigations suggest that serum osteopontin levels could be used to discriminate between persons with exposure to asbestos, who do not have early pleural mesothelioma, and those with exposure to asbestos, who do have early pleural mesothelioma.¹⁴ However, other malignant tumours have

elevated levels of osteopontin, thus the measurement of this serum marker has not proven enough specificity.

The definitive diagnosis of pleural mesothelioma is based on the positivity of biomarkers and tissue biopsy.¹⁵ All mesothelioma tumours have positive immunohistochemical staining for

Figure 5 Histopathological analysis of a wedge resection of lung parenchyma. (A) H&E, ×10 showing atypical infiltrative mesothelial cells with papillary arrangement. The immunohistochemistry stain (B) positive for calretinin and (C) negative MOC-31.

Figure 6 Positron emission tomography/CT scan showing diffuse fluorodeoxyglucose-avidity in the right pleura.

pancytokeratin, moreover when other negative metastatic sources should be considered, such as malignant melanoma and malignant lymphoma.⁴ A panel of both positive and negative stains is required to make a reliable diagnosis.¹⁶ Epithelial tumour markers such as WT-1, calretinin, podoplanin and keratin 5–6 are positive in 70–90% of mesotheliomas. In opposition, carcinoma tissue markers, such as MOC-31, BG8, CEA, TTF-1 and CD15, have been very useful in differentiating mesotheliomas from adenocarcinomas of the lung.^{16 17}

Recent studies on tumour markers have demonstrated the upregulation of GLUT-1 transporter proteins in tumours such as mesothelioma, making it a new promising marker of malignant transformation.¹⁸

The median survival after the diagnosis of pleural mesothelioma is 9–12 months.² The main pretreatment determinants of poor prognosis established by the Cancer And Leukaemia Group B (CALGB) were defined as pleural involvement, lactate dehydrogenase (LDH) over 500 IU/L, poor performance status, chest pain, platelet count >400 000/ μ L, non-epithelial histology and age >75 years.¹⁹

Although palliative care has been the primary goal of the treatment for pleural mesothelioma.³ This multimodality approach includes surgical, radiation and chemotherapy treatment. Surgical pleurodesis is effective in controlling symptoms of recurrent pleural effusion. Radiation therapy reduces pain and symptoms of dyspnoea, but implies large exposure field. Combined chemotherapy regimens have demonstrated variable palliative benefit in terms of the overall quality of life, most of

them being anthracycline-based combinations or platinum-based combinations.²⁰

The rapidly emerging understanding of the biology and tumour markers of pleural mesothelioma has been leading to trials of molecular targeted therapies, without definitive conclusion thus far.

Learning points

- ▶ People with malignant pleural mesothelioma can and do present to a wide range of physicians as a chest radiograph abnormality.
- ▶ Asbestos is thought to be the single most important risk factor for the development of mesothelioma.¹ This relationship has been described since 1955,³ and the mean latency period after exposure is 35–40 years. Approximately 8% of deaths in asbestosis workers exposed to greater than OSHA-PEL (0.1 fibres /cm³×8 h).
- ▶ Median survival after the diagnosis of pleural mesothelioma is 9–12 months.² The main pretreatment determinants of poor prognosis established by the Cancer And Leukaemia Group B (CALGB) were defined as: pleural involvement, LDH over 500 IU/L, poor performance status, chest pain, platelet count >400 000/mcl, non-epithelial histology and age >75 years.¹⁹
- ▶ Mesotheliomas frequently present as unilateral, plaque like or nodular pleural thickening.¹ A slight right-sided predominance is observed, possibly because of a larger pleural surface area.¹ Between the relatively small number of cases in which the tumour locates in the mediastinum, most are associated to a pericardial origin.
- ▶ Surgical management may represent the only opportunity of cure for patients with malignant mesothelioma, the evidence supports that pleurectomy/decortication or pleuropneumectomy in the treatment of malignant pleural mesothelioma has high recurrence rates and frequent postoperative complications.^{3 21} Although prognosis is guarded, timely diagnosis can reduce misattribution of symptoms, mistreatment and improve quality of life through timely institution of palliative care.

Table 1 Tumour markers in pleural malignant mesotheliomas

Positive tumour markers	Negative tumour markers
Pancytokeratin	MOC-31
CYFRA 21-1	BG8
TPA	CEA
WT-1	TTF-1
Calretinin	CD15
Podoplanin	CA 15-3
Keratin 5/6	CA 15-9

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Aziz F. Radiological findings in a case of advance staged mesothelioma. *J Thorac Dis* 2009;1:46–7.
- 2 Ferlay J, Bray F, Pisani P, et al. *Cancer incidence, mortality and prevalence worldwide IARC cancerbase No.5, version 2.0 Lyon*. France: IARCH Press, 2004.
- 3 Pistolesi M, Rusthoven J. Malignant pleural mesothelioma: update, current management, and newer therapeutic strategies. *Chest* 2004;126:1318–29.
- 4 Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2009;133:1317–31.
- 5 Broadus VC, Everitt JJ, Black B, et al. Non-neoplastic and neoplastic pleural endpoints following fiber exposure. *J Toxicol Environ Health B Crit Rev* 2011;14:153–78.
- 6 Marinaccio A, Binazzi A, Marzio DD, et al. Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. *Int J Cancer* 2012;130:2146–54.
- 7 Muscat JE, Wynder EL. Cigarette smoking, asbestos exposure, and malignant mesothelioma. *Cancer Res* 1991;51:2263–7.
- 8 Jasani B, Gibbs A. Mesothelioma not associated with asbestos exposure. *Arch Pathol Lab Med* 2012;136:262–7.
- 9 Bagheri R, Haghi SZ, Rahim MB, et al. Malignant pleural mesothelioma: clinicopathologic and survival characteristic in a consecutive series of 40 patients. *Ann Thorac Cardiovasc Surg* 2011;17:130–6.
- 10 Tomasetti M, Santarelli L. Biomarkers for early detection of malignant mesothelioma: diagnostic and therapeutic application. *Cancers* 2010;2:523–48.
- 11 Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:1541–9.
- 12 Hollevoet K, Nackaerts K, Thimont J, et al. Diagnostic performance of soluble mesothelin and megakaryocyte potentiating factor in mesothelioma. *Am J Respir Crit Care Med* 2010;181:620–5.
- 13 Schneider J, Hoffmann H, Dienemann H, et al. Diagnostic and prognostic value of soluble mesothelin-related proteins in patients with malignant pleural mesothelioma in comparison with benign asbestosis and lung cancer. *J Thorac Oncol* 2008;3:1317–24.
- 14 Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. *N Engl J Med* 2005;353:1564–73.
- 15 Aziz T, Jilaihawi A, Prakash D. The management of malignant pleural mesothelioma; single centre experience in 10 years. *Eur J Cardiothorac Surg* 2002;22:298–305.
- 16 Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. *Chest* 2009;136:888–96.
- 17 Astoul P, Roca E, Galateau-Salle F, et al. Malignant pleural mesothelioma: from the bench to the bedside. *Respiration* 2012;83:481–93.
- 18 Kato Y, Tsuta K, Seki K, et al. Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma. *Mod Pathol* 2007;20:215–20.
- 19 Herndon JE, Green MR, Chahinian AP, et al. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. *Chest* 1998;113:723–31.
- 20 Roberts JR. Surgical treatment of mesothelioma: pleurectomy. *Chest* 1999;116:446S–9S.
- 21 Takagi K. Pleuropneumectomy: an effective treatment modality for malignant pleural mesothelioma? *Ann Thorac Cardiovasc Surg* 2008;14:135–7.

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