Malignant Pleural Mesothelioma

K Rishikesh¹, U Kini², N Shenoy¹, B Joy³, G D’Souza⁴, A Shet¹

Abstract
Malignant pleural mesothelioma is a rare neoplasm which arises from pleural surface. Most patients present with locally advanced or metastatic disease in which the overall outcome is poor. We report a case of a female with the history of early stage tongue cancer cured 20 years previously with surgery and radiotherapy who presented with chest pain and was found to have metastatic malignant pleural mesothelioma. The presentation, diagnostic work up, and management of this interesting case is discussed and the current literature pertaining to mesothelioma is reviewed.

Introduction
Mesothelioma is a rare neoplasm that arises most commonly from the mesothelial surface of pleural and peritoneal cavities, tunica vaginalis or the pericardium, commonly presenting in the fifth to seventh decades of life.¹ The predominant cause of malignant pleural mesothelioma (MPM) is inhalational exposure to asbestos. We present an unusual case of a 45 year old lady with a history of carcinoma base of tongue, cured 20 years prior to presentation, with no apparent history of asbestos exposure, who was ultimately diagnosed with malignant pleural mesothelioma. The approach to the diagnosis of this challenging case is presented and the management of malignant pleural mesothelioma reviewed.

Case Report
A 45 year old lady with a past history of adenocarcinoma of the base of the tongue (T2 N2a Mx), low grade polymorphous type, with cervical lymph node metastasis and extracapsular spread post excision, combined with bilateral radical neck dissection and radiotherapy 20 yrs prior, presented to the hospital for the evaluation of mild left sided chest pain. The pain was of gradual onset, slowly progressive, persistent, pleuritic in nature, and associated with mild cough without expectoration. She denied fever, exertional dyspnea, orthopnea, wheezing, paroxysmal nocturnal dyspnea (PND), and pedal edema. She also admitted to unintentional weight loss of approximately 4 kgs over a period of four months. She was a non-smoker and denied any occupational or environmental exposure to asbestos.

Examination revealed a thin asthenic woman with a low BMI, who was in no apparent respiratory distress. Examination of the neck revealed a small 1x1 cm, hard, non-tender and mobile swelling in the left supraclavicular region. The surgical scars of bilateral neck dissection along with radiation induced skin changes were noted. No lymph nodes were detected in the axillary or inguinal region. General examination was otherwise unremarkable. The respiratory system examination was consistent with the left sided pleural effusion.

Chest X-Ray was consistent with left side pleural effusion. Laboratory investigations were significant for a mild anaemia of 10.4 g/dl, elevated platelet count of 540,000/µl and ESR of 101mm in the first hour. A diagnostic pleural aspiration revealed exudative effusion with mesothelial cells and a few atypical cells. Fine needle aspiration cytology of the left supraclavicular swelling suggested a malignancy. Since recurrent carcinoma of tongue was thought unlikely due to the large time interval, a CT scan of the chest was performed which revealed pleural effusion, multiple left side pleural based and bilateral lung parenchymal nodules, widespread rib and vertebral erosions (Figure 1). Subsequently, a whole body positron emission tomography scanning revealed a highly metabolically active, diffuse nodular thickening of left pleura with associated pleural effusion, multiple metabolically active mediastinal lymph nodes, and a few right parenchymal lung nodules. Unsurprisingly, there was no evidence of recurrent mass in the tongue or cervical lymphadenopathy. The patient underwent video-assisted thoracic surgery, which showed multiple pleural based nodules, pleural thickening, and pericardial involvement. Pleural biopsy showed an infiltrating neoplasm with a tubulopapillary pattern with cuboidal neoplastic cells having eosinophilic to vacuolated cytoplasm and vesicular nuclei (Figure 2A and B). This histopathology was suggestive of malignant mesothelioma – epithelioid variant. The immunohistochemistry panel (Figure 3A and B) with positivity for calretinin, WT-1, CK5/6 and negative for TTF-1 and CK 20 confirmed the diagnosis. The patient was thus diagnosed with advanced surgically unresectable malignant mesothelioma (T3N3M0) and was treated with palliative doublet chemotherapy consisting of Pemetrexed and Cisplatin. After receiving three cycles of chemotherapy she improved clinically and radiologically but was subsequently lost to follow-up.

Discussion
Malignant pleural mesothelioma is a rare neoplasm with increasing incidence in developing countries due to exposure to asbestos.¹ Our patient had no known history of asbestos exposure, which may be in part due to decreased awareness or poor occupational health control measures with respect to asbestos exposure in India. The patient presented with hard supraclavicular nodule and pleural effusion that could have been either due to recurrence of carcinoma of tongue or due to primary lung or pleural malignancy with metastasis. The probability of recurrence in comparison to a second malignancy was low considering the 20 year disease free period from the initial squamous cell cancer. While radiation therapy to supradiaphragmatic lung fields in cases of lymphoma, testicular cancer and rarely in breast cancer is a known risk factor for development of mesothelioma, neck radiation following...
carcinoma tongue is not similarly associated in the published literature.

Pleural mesothelioma as seen in India, most commonly presents in fifth to seventh decades of life. The onset is slow and insidious being associated with continuous nonpleuritic chest pain with rapidly accumulating pleural effusion. Irregular pleural thickening involving parietal and visceral pleura with very minimal involvement of lung parenchyma and gradually encasing the lung by a thick rind of tumor is characteristic at radiology. It extends locally by contiguity into ribs and thoracotomy scars and metastasize in a centrifugal manner to surrounding local structures unlike primary lung carcinoma. While unusual, metastasis may occur to opposite lung, brain, and other extra thoracic sites. Metastatic disease can be accompanied by a variety of paraneoplastic syndromes including DIC, migratory thrombophlebitis, thrombocytosis, haemolytic anemia, hypoglycemia and hypercalcemia. Although our patient had undergone bilateral cervical lymph node dissection 20 yrs prior to presentation, presentation with a left supraclavicular mass that yielded malignant cells suggested either the presence of an apical pleural deposit or residual lymph node from an incomplete neck dissection, more likely the former. This patient also presented with metastasis to the opposite lung which has been described previously, although the finding is rare.

Diagnosis of MPM mandates a good history correlated well with physical examination, radiological findings, pleural fluid cytology histopathological examination of pleural nodule and its immunohistochemistry. Some studies suggest that PET-CT is superior to FDG-PET, MRI and CT in terms of specificity and sensitivity of disease detection and staging of MPM. The pleural fluid cytology seen in the present case showing cell aggregate exhibiting morulae, nuclear pleomorphism and cannibalism indicates mesothelial origin and probably needs radiological correlation to be called as mesothelioma. Hence there is limited role of cytology in the primary diagnosis of MPM. However, surgical pleural biopsy while invasive and associated with morbidity still provides the most accurate definitive diagnosis. Video assisted thoracoscopic biopsy has been considered most accurate in terms of diagnostic yield when compared with thoracocentesis, fluid cytology or closed pleural biopsy.

Differentiating mesothelioma from mesothelial hyperplasia is the first step in the approach to a pathological diagnosis of malignant mesothelioma. Disorganised growth, stromal/fat invasion and absence of inflammation favour the diagnosis of mesothelioma. Epithelioid malignant mesothelioma subtypes

Fig. 1: Axial CECT image of the chest in soft tissue window showing nodular enhancing posterior pleural based mass on the left side. There is destruction of the adjacent rib and vertebrae

Fig. 2: Photomicrographs showing tubulopapillary configuration of the infiltrating pleural mesothelioma with extensive stromal hyalinisation and focal myxoid changes (A) and higher magnification (B) shows bland morphology of the tumor cells inspite of patient being in stage IV disease
are composed of polygonal, oval, or cubical cells that often mimic non-neoplastic mesothelial cells. Sarcomatoid malignant mesothelioma consists of mostly spindle cells, as also in mixed or biphasic malignant mesothelioma. Positivity for EMA, p53, GLUT-1 on immunohistochemistry favour malignant mesothelioma as opposed to reactive mesothelioma. Staining for calretinin, keratin 5/6, WT-1 protein, podoplanin (D2-40) favours epithelioid variant of malignant mesothelioma. Adenocarcinoma involving lung is a common differential diagnosis and positive staining for MOC-31, BG8, CEA, B72.3, Ber-EP4, TTF-1, CD15(Leu-M1) are more suggestive of lung adenocarcinoma than malignant mesothelioma. Therefore, we are of the opinion that MPM is best diagnosed following thorough evaluation of all existant clinical and radiological data along with immunohistochemistry and follow-up studies.

Therapeutic options for malignant mesothelioma include surgery, chemotherapy and radiotherapy. Aggressive surgical intervention is generally not possible in vast majority of patients because of advanced disease at presentation and diffuse involvement of pleura. Typically, survival benefits post surgery are limited to a select few who present early, but in most cases the role for surgery is mostly limited to palliating the symptoms. Consensus statements favour surgery when possible, is best performed in conjunction with other forms of treatment (chemotherapy and radiation therapy) at centers that have expertise in this area.

The introduction of several novel drugs has resulted in better outcome following chemotherapy for the management of malignant mesothelioma. Gemcitabine, Pemetrexed, Anthracycline, Vinca Alkaloids have all been shown to have substantial activities but Cisplatin is the backbone of chemotherapy in this disease. Based on randomized controlled phase III studies, doublet therapy with a Cisplatin backbone either in combination with Pemetrexed or Ralitrexed is considered standard first line therapy for MPM.

MPM is considered resistant to radiotherapy. Therefore, radiation therapy is usually limited to local radiotherapy post surgery with doubtful surgical margins, or to prevent seeding of local tissues and sometimes for palliative care. Thalidomide, Molecular targeted therapies (gefitinib, imatinib and erlotinib) and immunotherapy (interferon and interleukins) have been tried with limited degree of success.

**Conclusion**

Malignant pleural mesothelioma can present in patients with no previous history of asbestos exposure. Radiological features that are inconsistent with primary lung cancer but showing pleural pathology should raise the index of suspicion of MPM. Correlating these findings with immunohistochemistry is mandatory and hence a diagnosis of malignant pleural mesothelioma requires systematic approach.

**References**