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A Case Series of Uncommon Causes of Malignant Pleural Effusion and its Implication on Patient Survival

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ABSTRACT

Malignant pleural effusion is associated with high morbidity, mortality, and a reduced quality of life. Palliative treatment is its only management with a mean survival ranging from 4-7 months depending on the stage and type of underlying malignancy. (37)

Over the past decade significant progress has been made in understanding the pathophysiology of MPE including its diagnostics, imaging and treatment.

In the current study we report four uncommon presentations of malignant pleural effusion and discuss its implications on patient survival.

We discuss a series of four cases of malignant pleural effusions, their uncommon aetiologies, varied clinical features, imaging, pleural and endobronchial appearance of malignant lesions and their histopathological appearances.

INTRODUCTION

The estimated number of incident cases of cancer in India for the year 2022 was found to be 14,61,427 (crude rate:100.4 per 100,000). In India, one in nine people are likely to develop cancer in his/her lifetime. (34)

The presence of malignant cells in the pleural fluid and/ or parietal pleura is known as malignant pleural effusion. It is one of the most common types of pleural effusion. Its occurrence signifies advanced disease and reduced life expectancy in patients with cancer. The most common causes of malignant pleural effusion are lung cancer, breast cancer and lymphoma. (35)

The role of pleural effusion in the prognosis of cancer can be seen in the seventh edition of the TNM staging classification by the American Joint Committee on Cancer, in which its status was changed from T4 to M1a. (37,36)

The mean survival of patients with cancer with malignant effusion ranges from 4 to 7 months and is dependent on the stage and type of the underlying malignancy. (38, 37) It can therefore be concluded that pleural effusion is a prognostic factor associated with a poor prognosis for patients with cancer.

CASE 1: Delayed breast cancer relapse with pleural metastasis and malignant pleural effusion

A 67-year-old female presented to the emergency department with dry cough, shortness of breath progressing from grade 2 to 4 MMRC over the last 3 weeks and left sided pleuritic chest pain for five days. She was a known case of diabetes mellitus and hypertension, well controlled on medication. 8 years ago, she had been diagnosed and treated for left-sided carcinoma of the breast with a modified radical mastectomy (MRM) followed by adjuvant chemotherapy and radiotherapy.

On general physical examination, there was no evidence of lymphadenopathy or any palpable masses. Breast exam also showed no palpable lymph nodes or lumps, a pigmented surgical scar was present over the left breast. Respiratory examination revealed absent breath sounds over the left infra-axillary and infra-scapular regions and decreased vocal resonance. Chest X-ray was performed and showed a moderate left-sided pleural effusion. CECT thorax was confirmative of left sided pleural effusion with multiple pleural nodules.

A diagnostic thoracentesis revealed haemorrhagic fluid which upon analysis showed a lymphocyte predominant, exudative effusion with a low ADA level (glucose 137 mg/dL, proteins 5.1 g/dL, and LDH 121 U/L). Cytology (cytospin) showed primarily reactive mesothelial cells and lymphocytes, along with a tiny cluster of enlarged hyperchromatic cells displaying marked nuclear overlapping. Differential diagnoses included tuberculosis, lung cancer, metastasis from an unknown primary source, sarcoidosis and chronic exudative effusions such as in rheumatoid arthritis.

Medical thoracoscopy was performed under conscious sedation with a left intercostal nerve block. It showed multiple grey-white nodular pleural deposits on the parietal pleura from which biopsies were acquired. Histopathological examination (HPE) revealed fragments of pleural tissue lined by mesothelial cells, along with an infiltrative lesion arranged in glands and papillae. The lesion was lined by polygonal cells with pleomorphic round to oval hyperchromatic nuclei and moderate cytoplasm. Immunohistochemical (IHC) staining showed positive for GATA3 in the lesional cells while TTF1 was negative. Calretinin highlighted the mesothelial cells, and oestrogen receptor (ER) and progesterone receptor (PR) staining showed strong intense positivity in 90% tumour cells (Allred score 5+3=8). Her2neu was negative and Ki67 showed 4% positivity.

The patient was diagnosed with metastatic breast cancer (TxN0M1 Adenocarcinoma, positive for oestrogen and progesterone receptors) and was referred to oncology where she was started on a chemotherapy regimen with paclitaxel.

DISCUSSION

Breast cancer is the most common leading cause of cancer-related death among women. While it carries a high risk of local and distant relapse or metastasis during the first decade after initial treatment, delayed relapse of breast cancer after 10 years of disease-free survival (DFS) is rare. Typically, breast cancer has a dual peaked relapse pattern, with most relapses occurring during the second and sixth to ninth years after initial treatment. (2)

Patients with stages I, Il, and III disease had a residual 5-year risk of recurrence of 7%, 11% and 13% respectively. (3)

The most common sites of breast cancer relapse are bone (70.6%) followed by liver (54.5%) and lung (31.4%). Breast cancer relapse and metastasis most commonly occur in the bone, liver, or lungs, especially with the ER +/HER2 breast cancer subtype 2. (12)

Breast cancer relapse remains a common cause of morbidity and mortality in patients who undergo initial treatment with surgery and with or without concurrent chemotherapy or radiation. Disease-free survival and overall survival depend on multiple factors, including the stage of the disease, hormone receptor status, age, and prescribed chemotherapy agents (2)

The median survival of MPE secondary to breast cancer metastasis is 15 months. (14)

Younger premenopausal women develop recurrence sooner and recurrence after decades is not so common (15). Patients with hormone receptor-positive tumours had a higher residual risk of recurrence than patients with hormone receptor- negative tumours regardless of menopausal status. (3)

There was also no association in the residual risk of recurrence between hormone receptor-positive patients who were treated with chemotherapy plus endocrine therapy vs those treated with endocrine therapy alone. (3)

In a study conducted by Abenna M Brewster et al, low-grade and positive hormone receptor status, which are associated with favourable short-term prognosis, were associated with a higher residual risk of recurrence. (3)

It has been shown that the survival advantage of hormone receptor-positive tumours is time dependent, because at longer follow-up, patients with hormone receptor-negative tumours have a survival rate that is similar to or more favourable than that of patients with hormone receptor positive tumours. (3)

The receipt of chemotherapy in addition to endocrine therapy did not influence the residual risk of recurrence; that patients with early-stage breast cancer who are disease free at 5 years after AST have a substantially increased residual risk of recurrence. (3)

Patients with hormone receptor-positive breast cancer remain at risk of recurrence for as long as they survive. For that reason, many investigators have explored the benefit of extended therapy beyond the standard treatment of 5 years. (4)

IMAGES

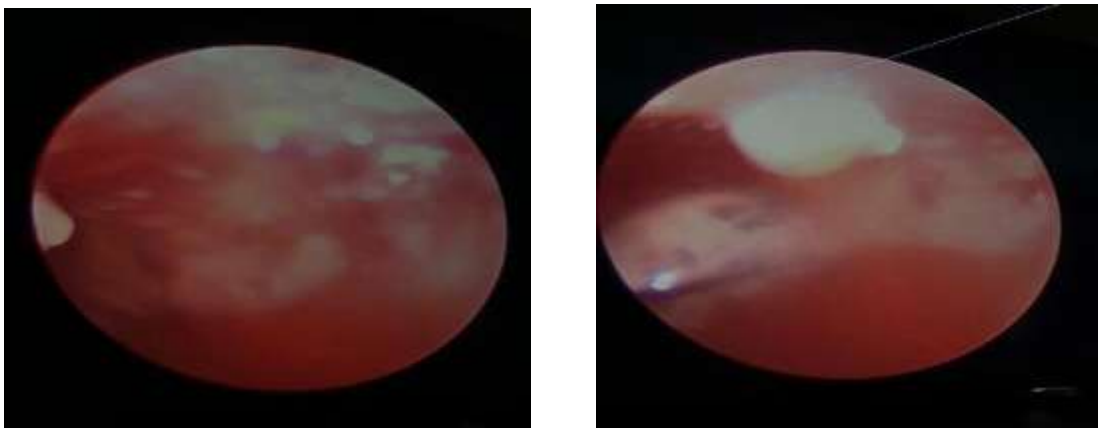

Figure 1A, 1B Thoracoscopic images of left parietal pleura showing multiple paleolar nodules measuring approximately 1cm

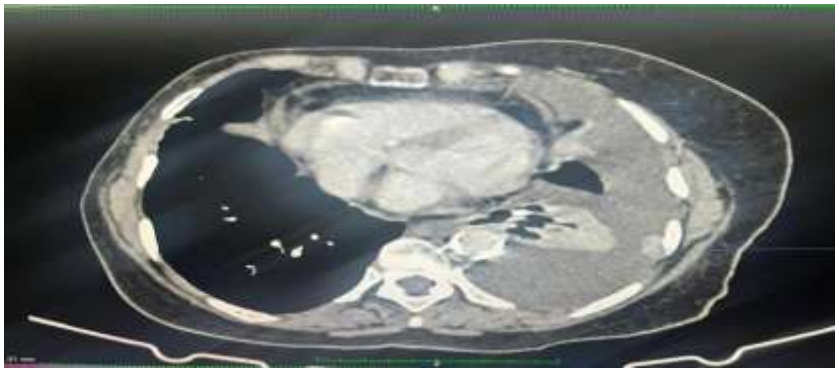

Figure 2 Axial section of CT showing left sided pleural effusion

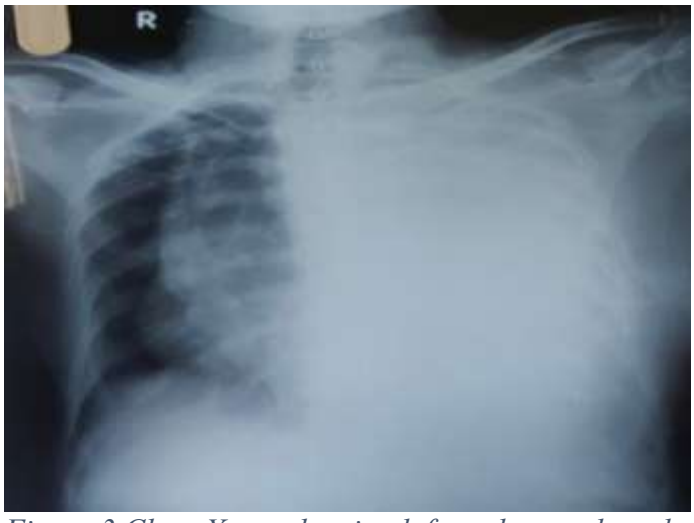

Figure 3 Chest X-ray showing left moderate pleural effusion

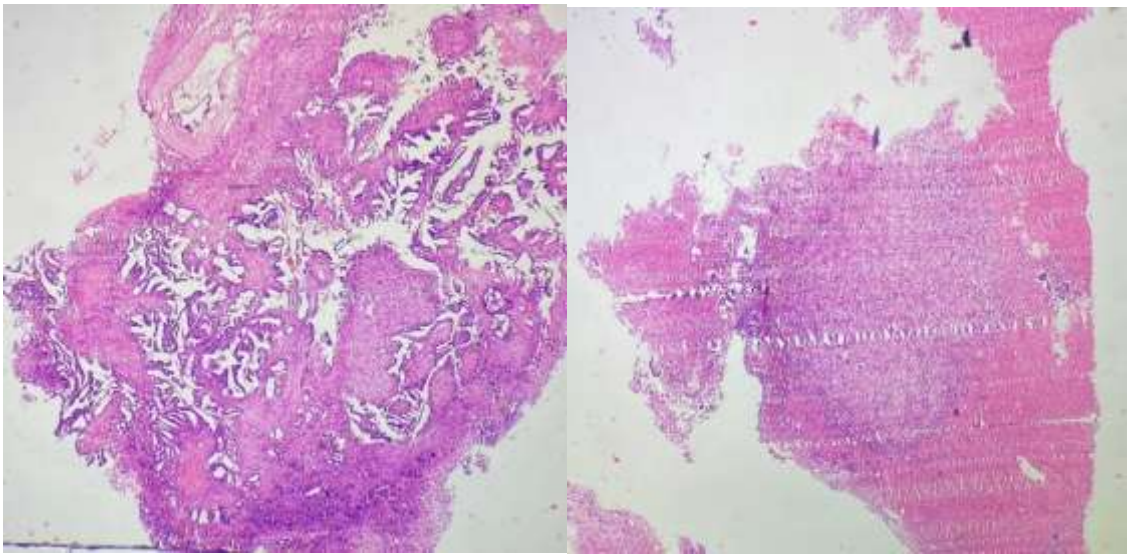

Figure 4 A, 4B, 4C Low power view of pleural biopsy showing glands and focal atypical cluster cells

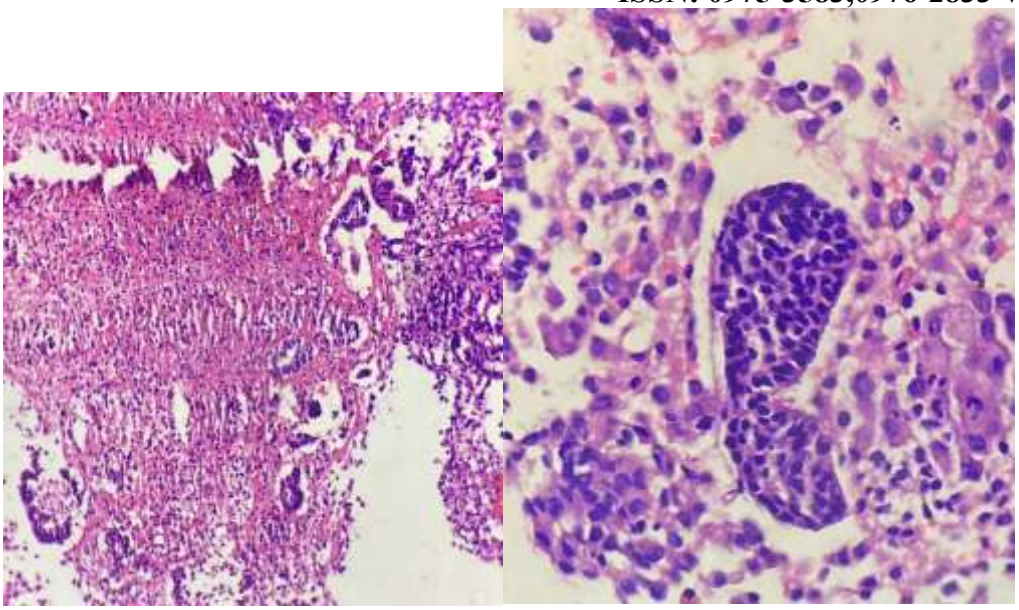

Figure 5A, 5B High power view showing cells arranged in glands and papillae, which are lined by polygonal cells with round to ovoid pleomorphic hyperchromatic nuclei and moderate to scant cytoplasm

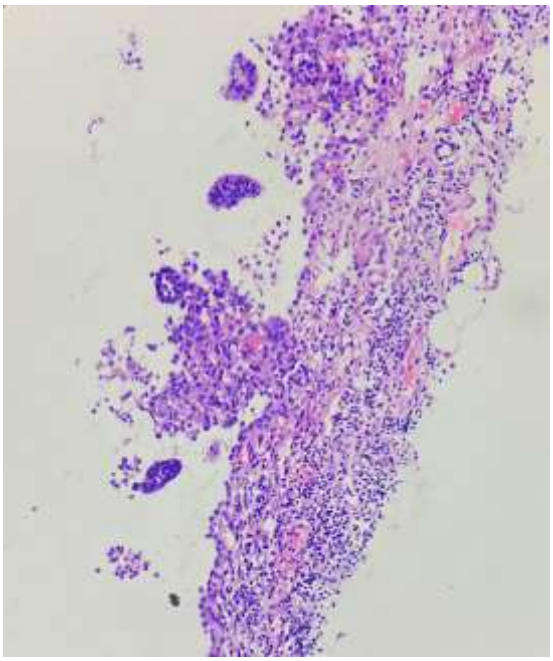

Figure 6 Pleural tissue lined by mesothelial cells

CASE 2: Ovarian cancer causing malignant pleural effusion

A 59-year-old female presented with a dry cough and shortness of breath progressively increasing from grade 2 to 3 MMRC over the past few weeks. She also had complaints of tightness in her chest and a left sided pleuritic chest pain for 3 days.

She was known hypertensive, and her condition was well controlled on routine medication. Breast exam revealed a mass in the left breast and right breast was normal. Respiratory exam showed absent breath sounds in the left infra scapular and infra-axillary areas.

Ultrasound of breast showed an irregular shaped hypoechoic lesion of 1 x 0.5 cm in the left breast and a normal right breast. Chest X-ray showed moderate left sided pleural effusion. CT scan confirmed the same.

Pleural fluid aspiration yielded haemorrhagic fluid which upon analysis showed a lymphocyte predominant, exudative effusion with a low ADA level. (LDH 1112 U/L, ADA 26 IU/L, sugars 38 mg/dL, and proteins 5 g/dL). Cytological analysis and cell block sections showed large atypical cells arranged in three-dimensional cell balls, acini and clusters, all scattered individually. Hyper chromatic nuclei with moderate to abundant cytoplasm were seen. These atypical cells were mixed with mesothelial cells, lymphocytes and neutrophils against a fibrinous background. Findings were consistent with a malignant pleural effusion.

Medical thoracoscopy was performed under conscious sedation with a serratus anterior plane block. Small white nodular lesions were visualised on the parietal pleura, and a sample for biopsy was procured.

PET scan revealed a right ovarian lesion with metastatic omental soft tissue deposits along with a nodular lesion in the upper inner quadrant of the left breast with multiple metastatic lymph nodes. Pleural effusion with left lower lobe consolidation and lesions in collapsed lung parenchyma were seen.

On IHC, WTI and PAX-8 were positive. Patient was diagnosed with stage 4 epithelial ovarian carcinoma and transferred to oncology where she was started on a chemotherapy regimen including paclitaxel and carboplatin.

DISCUSSION

When a person is diagnosed with Stage 4 ovarian cancer, the cancer has spread to the lungs or to the inner part of the liver, or to other distant sites. Cancer cells in fluid around the lungs are also considered Stage 4 ovarian cancer. (11)

The average relative 5-year survival rate for those diagnosed with distant spread ovarian cancer, which includes Stage 4 ovarian cancer, is about 31%. (11)

Among gynaecologic cancers, epithelial ovarian cancer (EOC) is second only to cervical cancer in incidence and number of deaths caused. (6, 17)

The pleural cavity constitutes the most frequent extra-abdominal metastatic site in ovarian carcinoma (OC). In patients with OC and pleural effusions, a positive fluid cytology is required for a stage IV diagnosis. (5) Patients with tumour extension into the pleural space have a median overall survival of 2 years. (5)

Circulation of peritoneal fluid throughout the abdomen and pelvis commonly results in diaphragmatic tumour implants, and in turn, peritoneal-pleural communication through the diaphragm may allow trans-diaphragmatic spread of tumour into the thorax. (6, 16)

Stage 4 ovarian cancer can be treated with neoadjuvant chemotherapy and, in patients who are candidates for optimal abdominal cytoreduction, thoracic debulking. (6, 18)

In addition, a recent study found that moderate-to-large pleural effusion on preoperative computed tomography (CT) was associated with a decrease in overall survival in patients with stage III or IV EOC after controlling for age, preoperative CA-125, surgical stage, ascites, and cytoreductive status. (19)

IMAGES

Figure 7A, 7B, 7C Thoracoscopic images of left pleural cavity showing multiple grey white pleural nodules measuring approximately 0.5 cm

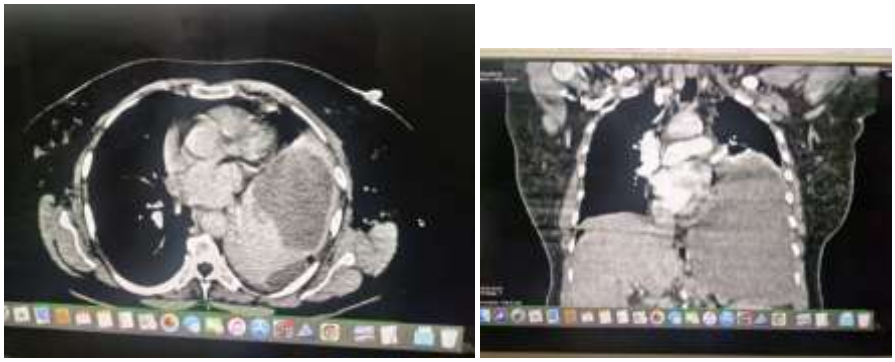

Figure 8A, 8B HRCT chest showing moderate left sided pleural effusion

CASE 3 Mesothelioma presenting as malignant pleural effusion

A 62-year-old female presented with complaints of decreased appetite, shortness of breath since the last 20 days, which was insidious in onset, gradually progressive from MMRC grade 2 to 3 and cough with mucoid sputum for one week. She also had pleuritic chest pain for 5 days. She was a known case of hypertension, well-controlled on medication, and bronchial asthma, for which she was not on any routine treatment.

On CT chest she was found to have moderate right sided pleural effusion. Thoracocentesis was performed and pleural fluid was sent for analysis. The yellowish haemorrhagic pleural fluid was lymphocyte predominant, exudative with a low ADA level (glucose 20 mg/dL, LDH 490 U/L, ADA 36.4 U/L).

Medical thoracoscopy was performed under conscious sedation with a left intercostal nerve block. It showed multiple grey-white nodular pleural deposits on the parietal pleura from which biopsies were acquired.

Smears showed many clusters of cells with large, round to oval vesicular hyperchromatic nuclei, small nucleoli, and scant to moderate vacuolated, eosinophilic cytoplasm surrounded by a background of lymphocytes, neutrophils, and proteinaceous, fibrinous material mixed with a few RBCs. Cytology suggested atypical and reactive mesothelial cells (IAC category 3).

On immunohistochemistry, it was found that the cells strongly expressed calretinin and were negative for TTF1 and PAX8. They were suggestive of papillary mesothelial proliferation. She was finally diagnosed with mesothelioma. She was referred to oncology for further management where she started on a chemotherapy regimen including pemetrexed and carboplatin.

DISCUSSION

MPE is the first clinical presentation of 90% of mesothelioma and 25% of lung cancer patients. (7,20)

Benign asbestosis pleural effusion (BAPE) is a plausible benign cause of an exudative effusion. BAPEs are often small, and patients are asymptomatic. Its natural history is one of chronicity with frequent recurrences. (7, 21)

Mesothelioma is a malignant neoplasm which causes dysfunction in the mesothelial cells of the lung pleura. It is insidious, presenting at Stages III-IV, with survival ranging from 4-19 months after diagnosis. (8)

Patients commonly present with cough, dyspnoea, fever, weight loss, and pleural effusions. Pleural effusions are usually right-sided, and about 5% present with bilateral pleural effusions. (8)

Pleural biopsies revealed malignant mesothelioma, epithelioid type positive for CK5/6, calretinin, and WT-1 with patchy weak staining for MOC-31. (8)

At the early stage of pleural mesothelioma, small nodules are found in the parietal pleura (not in the visceral pleura) that eventually extend along the pleural surface. Eventually, parietal and visceral pleura show adhesion, and the tumour encloses the entire lung parenchyma. In the case of a pleural mesothelioma, a tumour in the lung parenchyma suggests lung cancer with a pleural extension. There are three major types—epithelioid type, sarcomatoid type and biphasic type—and the proportion of each is approximately 60, 20 and 20%, respectively. (9)

In the case of epithelioid mesothelioma, calretinin, WT1, thrombomodulin, mesothelin and D2-40 can be applied as a mesothelial cell marker. In the case of sarcomatoid mesothelioma, cytokeratin (AE1/AE3 or CAM5.2 as antibodies) exhibits a high specificity and is the most useful. (9)

According to data from American cancer society the 5-year relative survival of a patient with malignant pleural mesothelioma is approximately 10%. (26)

In another article it was given that the prognosis of a patient with malignant pleural mesothelioma is generally poor with a median survival ranging from 8-14 months after diagnosis. (27)

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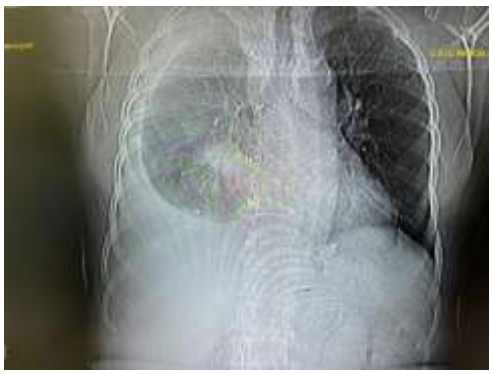

Figure 9 Chest X ray showing moderate right sided pleural effusion

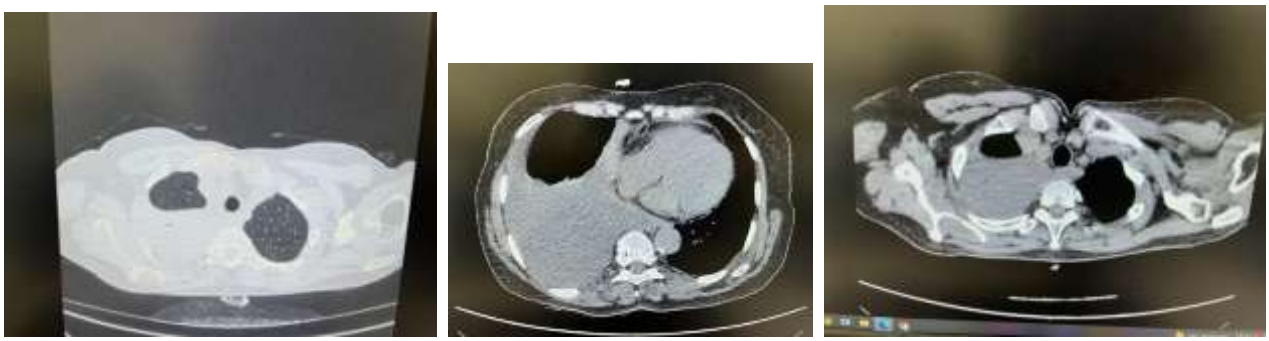

Figure 10A, 10B, 10C HRCT chest showing moderate right sided pleural effusion

CASE 4: Squamous cell carcinoma of lung causing malignant pleural effusion

An 81 year old male presented to the outpatient department with chief complaints of shortness of breath progressing from grade 2 to 3 MMRC in 2 months and left sided pleuritic chest pain for 7 days. He also had a cough which worsened over the past 2 weeks and was insidious in onset, gradually progressive with minimal mucoid non-foul-smelling sputum associated with streaky haemoptysis. It got worse lying down.

Postural variation was present and it increased on exertion. He also complained of a decreased appetite, disturbed sleep, and a weight loss of 7 kg over the past two months. Patient had no known comorbidities, but had a 40 pack per year history of smoking which he quit 10 years ago.

General physical examination showed pallor and grade 2 nail clubbing. On respiratory examination, there were absent breath sounds in the left mammary, infra-axillary and infra-scapular regions, along with reduced vocal fremitus in the left inter scapular region.

The differential diagnosis included lung cancer, tuberculosis, chronic aspiration pneumonia, post obstructive pneumonia due to foreign body or mass, and lipoid pneumonia.

HRCT chest revealed an ill-defined, heterogeneously enhancing soft tissue mass measuring 6.3 x 5.6 cm along with left minimal pleural effusion. The mass had areas of necrosis, spiculations, interstitial thickening and bronchial cutoff in the posterior basal segment of the left lower lobe, along with surrounding consolidation. These findings were suggestive of a neoplastic origin. Multiple centrilobular ground glass opacities with interstitial septal thickening were found in bilateral upper and left lower lobe (lymphangitis carcinomatosis). Multiple enlarged calcified mediastinal lymph nodes were found. In addition, a well-defined metastatic solid lesion was noted in the anterior limb of the left adrenal gland.

USG guided pleural fluid aspiration showed lymphocytic predominant educative effusion with low ADA levels. Bronchoscopy showed occlusion of the left main bronchus, significant luminal narrowing and a polypoidal growth at the 2 o'clock position. Endobronchial biopsy revealed a lesion composed of cells arranged in lobules and nests. The large polygonal cells had pleomorphic hyperchromatic nuclei and moderate eosinophilic cytoplasm. These findings were suggestive of a squamous cell carcinoma.

PET scan found distant metastasis to the left adrenal gland.

The patient was subsequently diagnosed with squamous cell carcinoma with metastasis to adrenal gland (T3N2M1b Stage 4A). She was referred to oncology where she was started on a chemotherapy regimen including paclixetal and carboplatin.

DISCUSSION

MPE is seen in about 15% patients with non-small cell lung carcinoma (NSCLC) and portends a poor prognosis. (22) Classified as stage IVA, median survival of lung cancer patients with MPE is four months, which is lower than malignant effusions metastatic from other primary sites. (10,23)

In addition, the prognosis of patients with subtypes of NSCLC with pleural effusions has not been compared. (10)

In a study conducted by Micheal Dorry et al, it had been demonstrated that the diagnostic sensitivity of pleural fluid cytology in NSCLC patients was lower for squamous cell carcinoma as compared to adenocarcinoma. (10) However, the yield differed based on the type of malignancy and they found

that the yield of pleural cytology was 78% in lung adenocarcinoma and 25% in squamous cell lung carcinoma. (10)

A study by Arnold et al. found an overall diagnostic yield of thoracentesis of 46% in MPE; the yield of lung adenocarcinoma effusions was 82% and squamous cell lung carcinoma was 14%. (14)

Squamous carcinoma cells have tight intercellular junctions and more robust anchors to the underlying basement membrane. (25)

This may lead to decreased shedding of squamous cells in pleural effusions as compared to bronchogenic adenocarcinomas. In addition, squamous cell carcinomas are more airway-centric, whereas adenocarcinomas are generally more peripheral in location which may allow easier spread to pleura. (25)

In a study from Surveillance Epidemiology and End Results (SEER), adenocarcinoma histology was associated with a better survival compared to squamous histology. These findings are consistent with the literature which shows that squamous cell carcinoma of the lung has a worse prognosis compared to lung adenocarcinoma. This could possibly be due to its significantly lower diagnostic yield from pleural fluid cytology and shorter median survival times. The median survival of patients with squamous cell malignant pleural effusion (MPE) was 112 days compared to 194 days in adenocarcinoma. (22)

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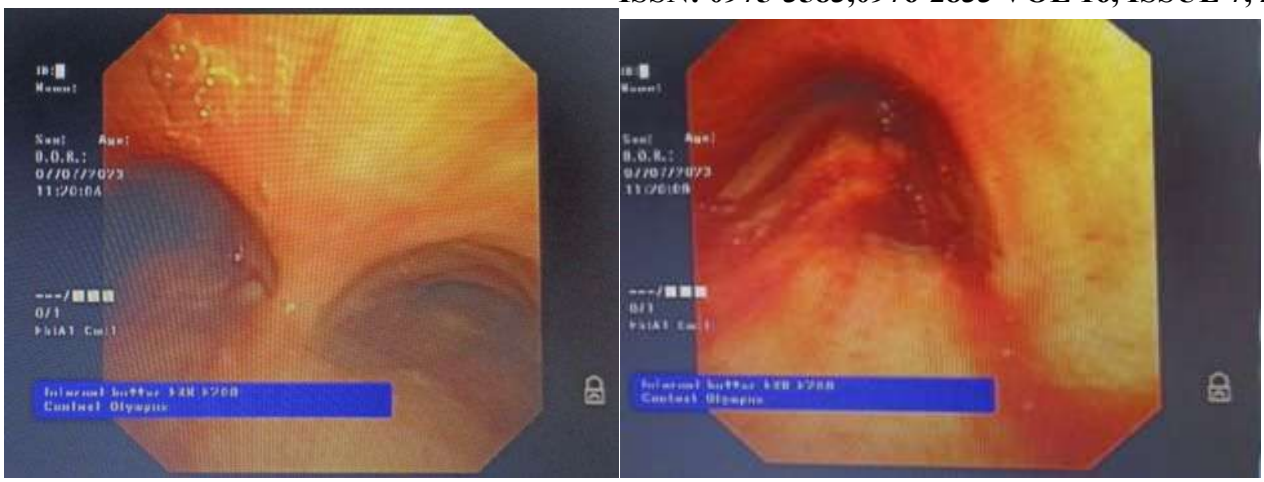

Figure 10A, 11BBronchoscpy showing occlusion of the left main bronchus, significant luminal narrowing and a polypoidal growth at the 2 o'clock position

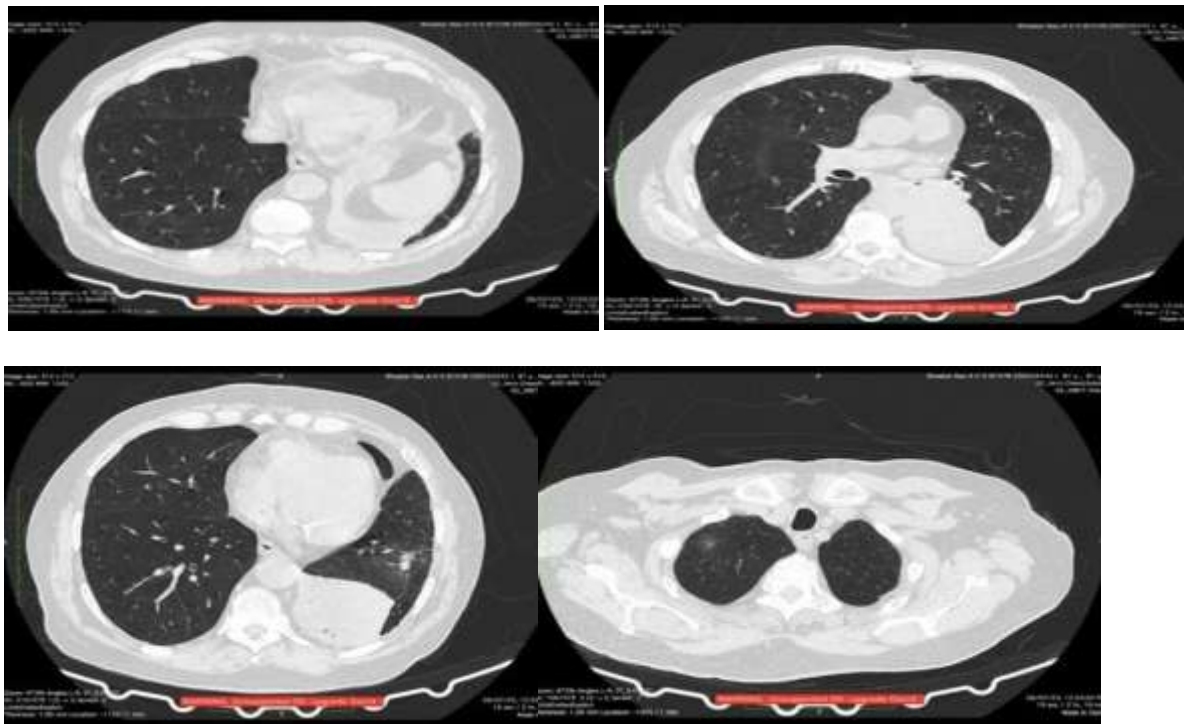

Figure 11A, 12B, 12C, 12D HRCT chest showing a heterogeneously enhancing soft tissue mass measuring 6.3 x 5.6 cm along with left minimal pleural effusion

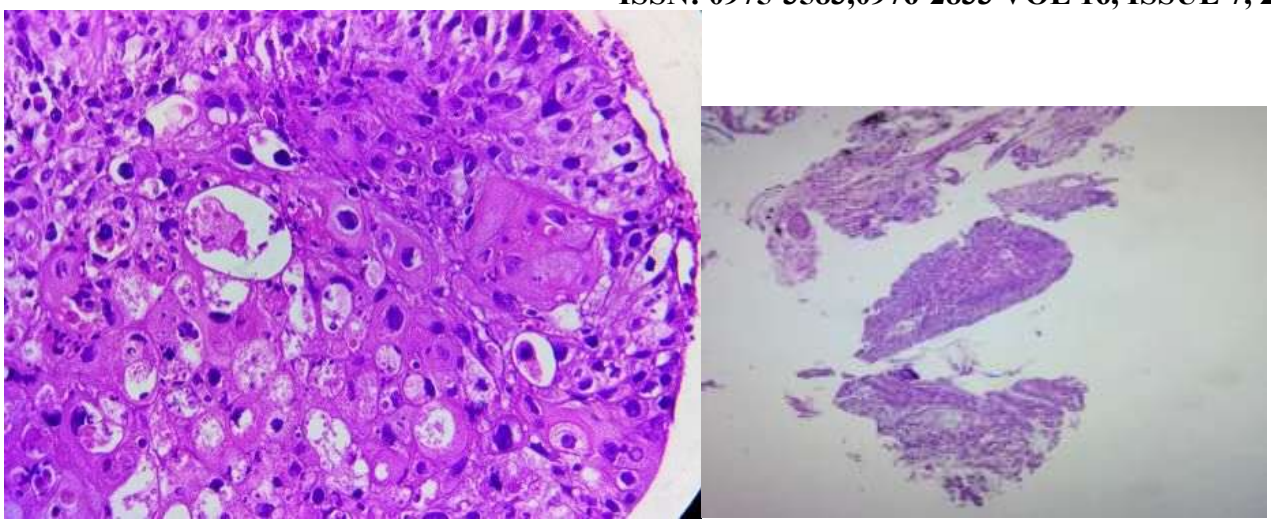

Figure 12A, 13B HPE showing large polygonal cells with pleomorphic hyperchromatic nuclei and moderate eosinophilic cytoplasm suggestive of squamous cell carcinoma

SUMMARY

Malignant pleural effusion can occur from metastasis from multiple primary sites- more commonly lung cancer, breast cancer, lymphoma, pleural mesothelioma and less commonly from ovarian cancer, stomach cancer, colon cancer and renal cell carcinoma.

MPE is associated with poorer survival and increased mortality. The median survival of a patient from diagnosis of malignant pleural effusion from breast cancer is 15 months (14), from ovarian cancer is 21 months (28), from mesothelioma is approximately 8- 14 months (27), and from squamous cell carcinoma is around 3 months (22).

It is evident that diagnosis of MPE carries a poor prognosis. Cancer screening has come up as a diagnostic modality for early detection of many cancers and helps in preventing cancer related death.

As a part of developing a screening mechanism for ovarian cancer, screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality (32)

From the data of two observational studies conducted among women undergoing screening mammography, it was found that there was a 30-40% drop in breast cancer mortality for women in their 40s. (29, 30)

According to the US National Lung Screening Trial (NLST), it was shown that computed tomography (CT) screening results in 20% mortality reduction in lung cancer patients. (31)

Being exposed to asbestos is the biggest risk factor for mesothelioma and this includes factory workers, miners, insulation manufacturers, installers, etc. Asbestos can also be found in some old buildings and poses a risk to its residents. However, there are no proven methods of screening that reduce mortality from mesothelioma caused by asbestos. (33)

CONCLUSION

The presence of malignant pleural effusion is a marker of poor survival and efforts like cancer screening have to be utilised wherever implicated to diagnose malignancies at an earlier stage so as to prevent cancer related death.

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