Original Article

Malignant Pleural Mesothelioma: An Under Diagnosed Entity
Review of 15 cases of Malignant Mesothelioma

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Objective: Malignant Mesothelioma is a highly aggressive tumor that can arise from pleura, peritoneum or tunica vaginalis. In more than 80% cases it involves pleura and is related to asbestos exposure. The rarity of malignant pleural mesothelioma (MPM) makes it unfamiliar to many physicians leading to unnecessary delays in diagnosis and treatment. A misdiagnosis will obviously reduce the chance of survival. While mesothelioma is widely talked about now, still it is considered rare tumor in our country and is frequently misdiagnosed. The objective of this study is to emphasize that mesothelioma is not that rare and doctor should always reassess his diagnosis when a patient does not respond to otherwise effective therapy.

Methods: It is an observational retrospective study. We reviewed 15 cases of MPM diagnosed from 2014-2017. We evaluated initial diagnosis, age, sex, profession, presenting complaints, CT chest/PET CT, Tumor markers and stage of MPM at the time of diagnosis.

Results: Out of 15 patients 9 were males and 6 were females. Mean age of patients was 55 years(35-64). Average duration of symptoms was 6.5 months. All patients had fever, shortness of breath and weight loss while 12 patients (80%) had severe chest pain and cough as well. Ten (66%) patients had an initial diagnosis of tuberculous pleural effusion and were taking antituberculous treatment, 4 (27%) patients had recurrent pleural effusion of unknown etiology and one patient (7%) was treated as empyema. All 6 females were housewives but men had different professions. Eleven (73%) patients had left sided and 4 (27%) had right-sided pleural effusion. Pleural fluid analysis in 11(73%) patients was exudative lymphocytic, 3 (20%) had transudative lymphocytic while one (7%) patient had frank pus. In All cases pleural fluid was negative for AFB smear and culture. Few atypical cells were seen in one patient and malignant cells were reported in one case. Three(20%)patients had PET CT, which showed diffuse hyper metabolic thickened pleura with lymphadenopathy and bone involvement. Twelve (80%)patients had conventional CT chest, all showing diffuse pleural thickening & lymphadenopathy while 2 (13%) had evidence of rib erosions as well. Video assisted thoracoscopy (VATS) was done in all patients, which revealed multiloculated pleural effusions with pleural thickening studded with multiple nodules. Pleural biopsies from all these patients were cytokeratin AE1/AE3 (strong positive), cytokeratin CAM5.2 (strong positive), cytokeratin7 (positive), Calretinin (focal positive),WT-1(focal positive),HBNE-1(focal positive) suggestive of malignant mesothelioma. Six (40%) patients had stage III, while 9 (60%) patients had stage IV disease.

Conclusions: This study highlights that though malignant mesothelioma is considered to be a rare malignancy but it is not that rare and we should not completely forget about it. We should reassess our diagnosis when patient does not respond to standard treatment otherwise effective.

Keywords: Malignant mesothelioma, pleural effusion, asbestos.

Introduction

Malignant pleural mesothelioma is a highly aggressive and one of the most lethal cancers with extremely poor prognosis. Median survival is not more than one year.[1] Incidence varies among different countries depending upon industrial and environmental exposure to asbestos.[2] In 70-80% cases it is associated with asbestos exposure. Asbestos fibers have tremendous thermal and electrical stability and are non-inflammable. It exhibits enormous tensile strength. All these properties make it a very usefulindustrial material for manufacturing of insulation, roofing and building products. Asbestos is classified into two main families, the serpentines and the amphiboles. The risk of mesothelioma has previously been correlated with fiber type but now according to the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), all types of asbestos are classified as class I carcinogens and exposure to

Asbestos is the major cause of both pleural and peritoneal mesothelioma.[3] In around 20% mesothelioma cases asbestos exposure is not documented, and viral oncogenes, ionizing radiation and genetic predisposition and nanomaterial (nanotubes) are blamed upon.[4,5] It is seen mostly in 5th and 6th decades of life. More commonly seen in men than women perhaps due to professional exposure. It can present with cough, chest pain, shortness of breath, fever and weight loss. The approach to this disease remains complex in terms of diagnosis, staging and treatment. The diagnosis is challenging because it mimics many other diseases clinically and histologically like pleural metastases, primary lung cancer, reactive pleural diseases and other pleural malignancies. Histopathologically three subtypes, epithelioid, sarcomatoid, and biphasic MPM are seen.[6] Detection of immune markers by immunohistochemistry (IHC) helps in diagnosis. Gold standard forepitheliod and biphasic MPM diagnosis is a combination of two positive and two negative immunehistochemical tumor markers. Sarcomatoustype does not show any specific markers that make its diagnosis even more challenging. Treatment options depend mainly on TNM stage of the tumor. MPM is a relatively chemo and radioresistant malignancy. Pemetrexed-platinum combination represents the standard of care as first-line treatment for patients with MPM. Surgery remains an option only in limited cases where early diagnosis could be made.[7] Rapid and early diagnosis is crucial for better prognosis of malignant mesothelioma. MPM is often misdiagnosed or there is a significant delay in diagnosis especially in developing countries like Pakistan where its rarity makes it unfamiliar to many physicians. Though there is a significant rise in the number of mesothelioma cases but still physicians are more tuned towards misdiagnosing it as tuberculosis, which is fairly common here.

Fifteen cases of malignant pleural mesothelioma were reviewed and analyzed various aspects of these cases.

Methods

It's an observational retrospective study. We reviewed 15 cases of MPM presented in Services hospital and Jinnah hospital Lahore in 2014 - 2017. Data was collected from medical files. Patients were diagnosed on VATS pleural biopsy .We evaluated initial diagnosis, age, sex, profession, presenting complaints, CT chest/PET CT, Tumor markers and stage of MPM at the time of diagnosis

Results

Out of 15 patients 9 (60%) were males and 6(40%) were females **(Table1).** Mean age of patients was 55 years (range, 35 to 64). All 6 females were housewives but men had different professions (Table 2).Average duration of symptoms was 6.5 months and all patients had fever, SOB and weight loss while 12 patients (80%) had chest pain and cough as well **(Table-3).**

Table-1: Gender distribution.

Characteristics		n=15	Percentage
Gender	Female	09	60
	Male	06	40
Age	Average age 55 years		(Range 36-64)

Table-2: Professions of the patients.

Gender	N=15	Profession
Females	06	All house wives
Males	09	
	01	Carpenter
	01	Plumber
	01	Sweeper
	01	Accountant
	01	Gas Station Worker
	01	Security Gaurd
	01	Laborer
	01	Construction worker
	01	Bank Manager

Table-3: Symptoms and initial diagnosis.

Symptoms	Weights loss	15	100
	SOB	15	100
Initial Diagnosis	Fever	15	100
	Cough	12	80
	Chest Pian	12	80
	Tuberculous Pleural Effusion	10	66
	Unknown etiolog	4	27
	Empyema	1	7

Ten patients (66%)had an initial diagnosis of tuberculous pleural effusion, and were taking anti tuberculous treatment, 4(27%) patients had recurrent pleural effusion of unknown etiology and one patient (7%) was treated as empyema **(Table-3).** Eleven patients(73%) had left sided & 4 patients (27%) had right-sided pleural effusion. Pleural fluid analysis was exudative lymphocytic in 11 patients (73%),transudative lymphocytic in 3(20%) while one patient (7%) had frank pus **(Table-4).** In all cases pleural fluid was negative for AFB smear and culture. Atypical cells were documented in one patient while malignant cells were seen in only one patient (6%).

Twelve (80%) patients had conventional CT chest, all showed diffuse pleural thickening and mediastinal

Table-4: Characteristics of pleural effusion.

Characteristics	n = 15	%
Left sided pleural effusion	11	73
Right sided pleural effusion	4	27
Exudative lymphocytic	11	73
Transudative lymphocytic	3	20
Frank pus	1	7
AFB smear and C/S	0	0
Pyogenic C/S	Growth of staph in case	6.6
Atypical cells	4	6.6
Malignant Cells	1	6.6

Table-5: CT Scan chest findings.

Radiology	n=15	Findings
Converntional CT Scan	11	Diffuse pleural thickening, nodules lymphadenopathy, rib erosion
PET Scan	3	Hyper metabolic thickened pleura with lymphadenopathy and bone involvement

Table-6: TNM Stage at the time of diagnosis.

Stage	n=15	%
Stage-I	0	0
Stage-II	0	0
Stage-III	6	40
VStage-IV	9	60

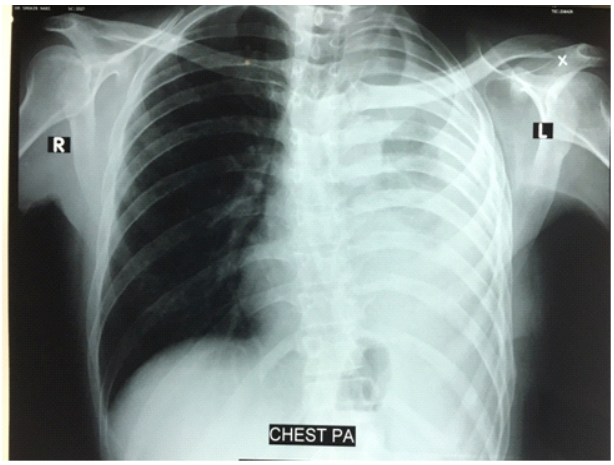

Fig-1: Xray chest showing almost opaque left hemithorax with no tracheal shift and residual aeration of left upper zone

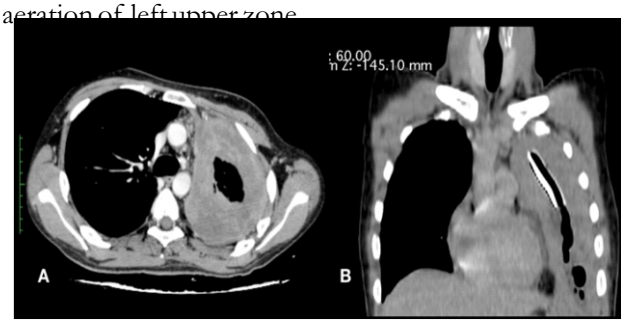

Fig-2: CT Scan chest- mediastinal window axial (A) and coronal (B) sections showing diffuse plural thickening encasing the left lung with associated volume loss

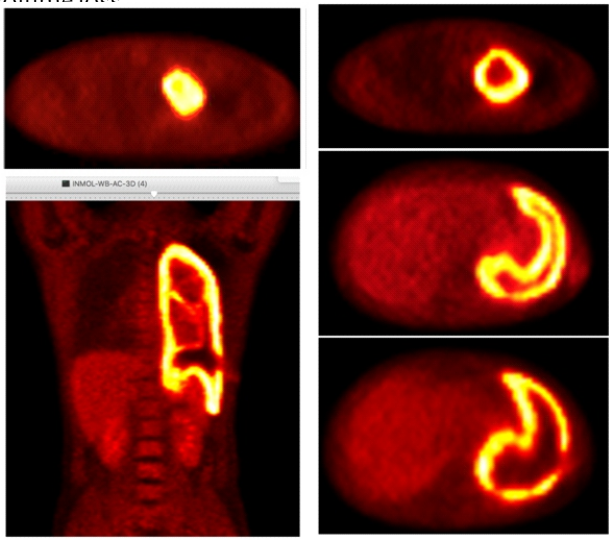

Fig-3: PETScan showing hyper metabolic pleural-based lesion encasing the entire lung parenchyma

lymphadenopathy while 2 (13%) had evidence of rib erosions as well **(Fig-2).** Three (20%) Patients had PET CT, which showed diffuse hyper metabolic thickened pleura with lymphadenopathy and bone involvement (**Table-5) (Fig-3).**Video assisted thoracoscopy (VATS) was done in all patients and almost all of them had multi loculated pleural effusions with pleural thickening studded with multiple nodules **(Fig-4).** Pleural biopsies from all these patients were cytokeratin AE1/AE3 (strong positive) cytokeratin CAM5.2 (strong positive) cytokeratin7 (positive), Calretinin (focal positive), WT-1 (focal positive), HBNE-1 (focal positive) suggestive of malignant mesothelioma. Six patients (40%) had stage III while 9 patients (60%) had stage IV disease **(Table 6).**

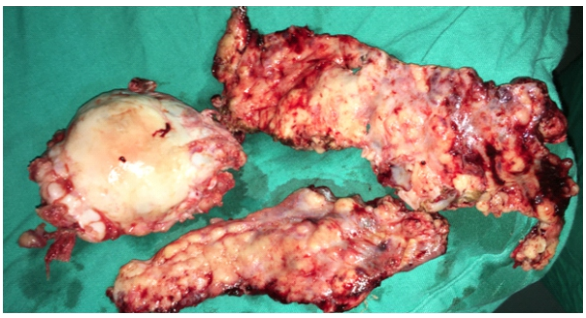

Fig 4: Resected tumor with multiple.

Discussion

Malignant pleural mesothelioma is a very aggressive malignancy and its intricateness poses a big challenge to pulmonologists and thoracic surgeons. Although asbestos exposure is the predominant risk factor for malignant mesothelioma but in around 20% cases asbestos exposure could not be established. In our study all 6 females were housewives and there was no direct or indirect exposure to asbestos. It is mentioned in literature that higher proportion of females who develop MPM is generally interpreted to reflect a higher rate of mesothelioma that is unrelated to asbestos exposure.[8,9]

Among males, only four (44.5%) had history of asbestos exposure due to their profession whereas in five males (55.5%) asbestos exposure was not found. Cases where asbestos exposure could not be established,non-occupational exposure should be considered. Exposure to mineral fibers in environment (e.g., erionite, a silicate fiber of the zeolite family) Viral oncogenes like Simian virus 40 (SV40), ionizing radiation and carbon nanotubes are considered to be possible causes of mesothelioma.[9,10] The average age of developing mesothelioma in our study was 55 years.

Unfortunately, the rate of mesothelioma misdiagnosis is quite high in Pakistan and is easily missed due to many reasons. As the doctors here do not frequently encounter it, they hardly suspect it. In this study out of 15 patients, 10 (66%) were diagnosed as tuberculous pleural effusion and were taking anti tuberculous treatment. Four patients (27%) remained undiagnosed and one patient was treated as empyema (Table-3).Empyema is a rare presentation of mesothelioma that has been documented in literature.[11] The diagnosis of malignant mesothelioma can be difficult because symptoms and clinical findings mimic common diseases like tuberculosis and primary or metastatic lung cancers, which are commonly encountered, by the local physicians and surgeons.

In our study all patients had fever, weight loss and SOB while 80% of them had chest pain and cough as well which can be easily attributed to any other chest disease. Chest x-ray was the first investigation that was done. It showed pleural effusion in all cases (Fig1). Left sided pleural effusion was seen in 73 % and right-sided pleural effusion in 27% cases though in literature predominantly right-sided pleural effusions have been reported.[12] CT scan remains the primary imaging modality for the evaluation of mesothelioma. Differentiation of MPM from metastatic pleural malignancies is difficult because their CT features are similar. Circumferential pleural thickening is considered to be more in favor of MPM.[13]

In most of our patients conventional CT chest was done that showed circumferential pleural thickening encasing the whole lung, multiple pleural mass / nodules and lymphadenopathy suggestive of fairly advanced disease (Fig 2). Only 3 Patients had PET CT, which showed diffuse hyper metabolic thickened pleura with lymphadenopathy and bone involvement (Fig 3).Fluid characteristics have no role in diagnosing mesothelioma. Fluid is exudative lymphocytic in most cases (73 % in our study) and malignant cells are difficult to detect in a fluid sample collected from around the lungs and thereby, pathologists will often miss the disease completely. In our study only in one case pleural fluid cytology revealed malignant cells **(Table 4).**

For an accurate diagnosis, a tissue biopsy is recommended, but the collecting process is more demanding. When a patient presents with a significant pleural effusion, thoracocentesis for cytology and

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