

## PLEURAL DISEASES IN THE MIDDLE EAST: A 2013 REVIEW

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DOI: 10.5455/ijmsph.2013.041220131

Received Date: 08.11.2013

Accepted Date: 24.01.2014

### ABSTRACT

Pleural pathologies in the Middle East are diverse and evolving partly due to steady immigration and increasing industrialization. Data about pleural diseases in the Middle East is relatively scarce. We are not aware of any review on this topic in current medical literature. This article aims at fulfilling this specific task. In this paper, we are reviewing selected English-written articles and publications in this field, from 1992 to 2011, using MEDLINE. Materials focusing on prevalence, etiologic factors, diagnostic techniques, and therapeutic interventions were included. In this review, we are categorizing pleural pathologies in five distinct sections: tuberculous effusions, parapneumonic ones, malignancies, transudative effusions, and a fifth category of miscellaneous conditions.

**Key-Words:** Middle East; Tuberculosis; Pleural Infections; Pleural Malignancies; Transudative Effusions

### Introduction

Most pleural diseases present with pleural effusion. It is defined as abnormal fluid accumulation in the pleural space. The spectrum of conditions that can potentially cause pleural effusion is very wide. Diagnosing any pleural effusion is usually based on clinical presentation, radiologic imaging, and laboratory findings post-thoracentesis. Treatment of any effusion is directly related to its cause and severity. Therapeutic interventions range from simple observation to major surgical intervention such as pleural decortication.

### Methodology

Opinions vary on the definition of the Middle East. A well-accepted definition describes it as the region where Asia, Europe and Africa meet.<sup>[1]</sup> Articles used for this review were selected by using MEDLINE to search for English-language articles published on pleural diseases from the Middle East. Keywords that were used for the search were: pleural effusion, pleuritis, pleural infection, empyema, pleural tuberculosis, and mesothelioma along with names of different countries using each country name separately. The period of the analysis was from 1992 to 2011, to include twenty years of published literature. All types of evidence including case reports were examined. The full text of all articles was examined. The research and the revision were done by the first two authors independently. Materials focusing on prevalence, etiologic factors, diagnostic techniques, and therapeutic interventions were included in the final review.

### Discussion

Review of pleural diseases studies from the Middle East shows five major etiological groups:

- Tuberculosis
- Infectious etiologies
- Malignancy
- Transudative effusions
- Other causes

#### TUBERCULOUS PLEURAL EFFUSION (TPE)

It is exudative lymphocytic pleurisy highly prevalent in this region. Pulmonary tuberculosis is indigenous to the Middle East and is known to be complicated by pleural dissemination. In the past three to four decades, and with workers' immigration from the Far-East and the Indian Subcontinent to the Gulf countries, more of these cases are diagnosed and treated. A Saudi paper reported that 67% of patients with tuberculosis were expatriates mainly from the Indian subcontinent & Yemen.<sup>[2]</sup> In a recent prospective study from Qatar, Khan and colleagues reported Tuberculosis as the leading cause of pleural effusion claiming around one-third of all case (32.5%) far ahead of pneumonia in second place (19%).<sup>[3]</sup> These findings confirm similar observations from more than a decade ago. Indeed, Saudi and Lebanese studies reported tuberculous etiology of 37% and 43.5% consecutively, ahead of all other causes of pleurisy.<sup>[2,4]</sup> In the Lebanese study, TPE was more frequent in the first five decades of life with 68.6% of patients being younger than 50 years of age. Similarly, patients with tuberculosis in the Saudi report were relatively young (mean age 33.4 years).

Iran seems to have a lower number of tuberculosis cases. In one study from Iran, a one-year period data were collected from 213 patients referred for pleural effusion. Tuberculosis was the third most common etiology of pleural effusion accounting for 5.2% of the total cases.<sup>[5]</sup>



**Figure-1:** Medical thoracoscopy view of parietal pleura in patient with tuberculous pleural effusion

Diagnosis of TPE can be elusive. It is best confirmed by presence of *Mycobacterium tuberculosis* in the pleural fluid, however, this is commonly difficult to achieve. In a Saudi study with 253 patients having TPE, positive pleural fluid microbiology was positive only one patient, while the yield with fluid culture and pleural biopsy were 10% and 68.5% respectively.<sup>[6]</sup> Other lab investigations that might aid in the diagnosis of TPE include elevated adenosine deaminase (ADA) level in the pleural fluid. The reported sensitivity and specificity of ADA in one study were 78% and 86% respectively.<sup>[7]</sup> Another test suggested in the diagnosis of tuberculous pleural effusion is the adapted T cell interferon gamma release assay. However, this test, using the QuantiFERON®-TB Gold In-Tube (GFT-GIT), was reported inaccurate by a recent Turkish study.<sup>[8]</sup> Closed percutaneous pleural biopsy was shown to have a diagnostic yield of about 50% in both Saudi and Kuwaiti studies. In the Saudi study, 122 pleural biopsies were performed on 116 patients with undiagnosed pleural effusions. Specific diagnosis was achieved in 49.1% of the cases with TB present in 31.8% of the pleural biopsies.<sup>[9]</sup> The Kuwaiti study had 143 patients and the overall diagnostic yield was 52%. Larger size biopsy sample (3 mm and more) and higher number of specimens (4 or more) improved the diagnostic yield.<sup>[10]</sup> In a small series of four patients, Karasulu and colleagues diagnostic yield reached 75% using semi-rigid thoracoscope.<sup>[11]</sup> The Role of medical thoracoscopy, a procedure done under local anesthesia with moderate sedation, in the management of

undiagnosed pleural effusions is gaining ground in this region. A local series of 14 cases, from the United Arab Emirates, was reported at the 2012 American Thoracic Society Conference. Pleural tuberculosis (Figure 1) was confirmed in 10 patients (72%), malignancy in 2 (14%), and chronic bacterial empyema in 2 (14%) patients.<sup>[12]</sup>

Some tuberculous effusions will be confirmed only by late cultures, while few others remain “negative”. In this region, experts usually advise early anti-tuberculous therapy initiation if clinical and radiological suspicions are high. The cornerstone of TPE therapy is management with prolonged quadruple standard anti-tuberculous medications. Cases of multi-drug resistant tuberculosis (MTB) or extensive drug resistant tuberculosis (XTB) are occasionally encountered. Corticosteroid therapy and therapeutic drainage seem to have no added benefit in the management of TPE.<sup>[13]</sup>

### PARAPNEUMONIC EFFUSIONS (PPE)

PPE in association with empyema, PPE are usually seen more with pediatric population of the Middle East. Of 492 reviewed pediatric cases with pleural effusion, more than 77% were PPE according to Utine et al.<sup>[14]</sup> In that study, microorganisms causing PPE were identified in 34.6% of patients. *Staphylococcus Aureus* and *Streptococcus Pneumoniae* were the two most common bacteria. These effusions are encountered in both community-acquired and nosocomial settings.

Diagnostic confirmation using direct pleural fluid staining and culture can be challenging in many cases especially with prior antibiotic use. One Turkish study reported their experience in patients with community-acquired pneumonia and PPE in the pediatric age group.<sup>[15]</sup> Ninety eight patients were retrospectively evaluated. The mean age was 6.5 +/- 3.5 years with 56% males. Preadmission antibiotic use was up found in 84% of patients. Blood cultures were positive in only 4%. 33.3% of the pleural effusion cultures were positive, with *Streptococcus Pneumoniae* being most common. PCR analysis is currently being used to improve the diagnostic yield of pleural fluid analysis. In another Turkish study of 28 consecutive pediatric patients with PPE, pleural fluid samples were obtained for Gram staining, routine culture and PCR analysis for *S. Aureus*, *S. Pneumoniae* and *H. Influenzae*. PCR analysis allowed detection of causative microorganisms in 35.7% of patients whereas pleural fluid cultures detected the etiological agent in only 7.1%.<sup>[16]</sup> In this region, raw milk consumption is still being practiced; diagnosing occasional case of brucella-induced pleurisy remains possible.<sup>[17]</sup>

Simple PPE usually will respond adequately to antibiotics without major sequelae. Complicated PPE and empyema are more difficult to treat and pleural drainage is usually required. Ozol et al. compared three interventions in 107 patients with complicated PPE: drainage with thoracentesis, drainage with chest tube insertion, and drainage with chest tube insertion and intrapleural streptokinase instillation. The success rates were 95.4%, 65.9% and 78.5% in groups 1, 2, and 3, respectively ( $P>0.05$ ).<sup>[18]</sup> In another study of PPE during childhood, successful fibrinolytic therapy prevented surgical operation in 22% of the patients who were candidates for surgical treatment.<sup>[19]</sup> The role of fibrinolytics in PPE continues to be evaluated by different studies.

### MALIGNANT PLEURAL EFFUSIONS (MPE)

MPE have a varying prevalence from country to country in the Middle East. Kalaajeh reported that MPE are second only to TPE in Northern Lebanon with a rate of 32.1%.<sup>[4]</sup> In that study, 88.7% of MPEs were due to lung cancer diagnosed more frequently among older age groups (73.6% were older than 50 years). This high prevalence rate of MPE was even worse in an Iranian study with 100 patients having exudative effusions. Heidari et al. reported that MPE etiology is ahead of TB with percentages of 43% & 33% of patients respectively.<sup>[20]</sup>

Histopathology of MPE also varies according to primary tumor and occupational hazards. Metastatic MPE is the most common form of malignant effusions.<sup>[21]</sup> Dağlı et al. reviewed 298 pleural fluid cases diagnosed with MPE. The most common cause of MPE was metastatic carcinomas including those from the lung, breast and ovaries, followed by malignant mesothelioma.<sup>[21]</sup> Exposure to tremolite asbestos or fibrous zeolite (erionite) in Southeast Turkey is well-documented. Malignant Pleural Mesothelioma (MPM) is common in this region.<sup>[22]</sup> Clinical symptoms such as chest pain, dyspnea, or weight loss remain non-specific. While simple Chest X-ray offers some helpful findings, Computed Tomography (CT) provides more helpful insights. One study reviewed the CT scan findings of 66 patients with MPM. Common findings were pleural effusion (80.3%), pleural thickening (77.2%), volume contraction (37.9%), involvement of mediastinal pleura (31.8%) and interlobar fissure (28.8%). Although none of these findings were pathognomonic for MPM, they were important in raising suspicion of MPM in patients with history of asbestos exposure.<sup>[23]</sup> The diagnosis of MPE is usually clinched by a combination of pleural fluid analysis and pleural biopsy. In the study by Heidari et al., the diagnostic sensitivity of closed pleural biopsy in patients MPE was 54% while the diagnostic sensitivity of pleural

fluid analysis was 70%. Combined pleural biopsy & pleural fluid analysis were positive in 91% of cases with MPE.<sup>[20]</sup> In another study of 124 patients, authors compared the diagnostic efficiency & reliability of Abrams needle pleural biopsy under CT scan guidance with that of medical thoracoscopy (figure 2).<sup>[24]</sup> In the CT-guided pleural biopsy group, the diagnostic sensitivity was 87.5% as compared with 94.1% in the thoracoscopy group ( $P = 0.252$ ). No difference was identified between the sensitivities of the two methods based on the CT scan findings and the degree of pleural thickening. However, study authors recommended the use of CT-guided pleural biopsy as the primary diagnostic method of in patients with pleural thickening or lesions observed by CT scan and the use of medical thoracoscopy in patients with only pleural fluid appearance on CT. The usefulness of tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA 15-3), carbohydrate antigen 19-9 (CA 19-9), and fibronectin in the pleural fluid was not proven.<sup>[25,26]</sup>



**Figure-2:** Medical thoracoscopy view of parietal pleura in patient with malignant pleural effusion

Thoracoscopic talc poudrage (TTP) and povidone-iodine pleurodesis (PIP) are two main therapeutic interventions currently offered for MPE.<sup>[27]</sup> In a prospective randomized control trial, Mohsen et al. compared the efficacy and safety of TTP versus PIP through a thoracostomy tube as a palliative treatment of MPE due to metastatic breast carcinoma. 22 patients received TTP (group A) while 20 patients (group B) underwent PIP through a thoracostomy tube as a bedside procedure. Both groups achieved good symptom-control with improvement in dyspnea. Post-procedure hospital stay was lower in group B ( $p=0.009$ ). At follow-up, the recurrence of significant pleural effusion requiring intervention was noted in 2 patients in group A and 3 in group B ( $p=NS$ ). PIP was recommended by the study authors as it is available, cost effective, safe, and can be repeated when necessary. Pleurectomy and



decortications are occasionally done for palliative reasons in selective cases of MPM.<sup>[28]</sup>

The prognosis of MPE remains poor despite such intervention. Ozyurtkan et al. investigated predictors of early mortality within three months in MPE in 85 patients. Predictors of early mortality included high-risk tumors (lung, stomach, soft tissue, bladder, esophagus, prostate, cervix, and lymphoma), poor performance status, and lower pleural fluid glucose concentration. The median survival was longer in renal cell, colorectal, breast, liver, ovarian and oropharynx carcinoma, and mesothelioma.<sup>[29]</sup> In cases of erionite-associated MPM and asbestos-associated MPM, the median survival after diagnosis was calculated at 13.52 and 21.56 months respectively.<sup>[30]</sup>

### TRANSUDATIVE EFFUSIONS

In a comparative analysis of the biochemical parameters used to distinguish between pleural exudates and transudates, the use of Light's criteria was able to classify 94.5% of the effusions correctly. The sensitivity and specificity were 99.3% and 87.6% respectively.<sup>[31]</sup> The specificity and accuracy to distinguish between pleural exudates and transudates improved further when combining pleural fluid cholesterol and lactate dehydrogenase levels.<sup>[31]</sup>

The exact prevalence of transudative pleural effusions is hard to estimate in the Middle East. There is wide regional variation as well as reporting of such conditions. It is likely that they are very common. Effusions due to congestive heart failure (CHF) seem to lead all transudates. In an Iranian study, these types of effusions were found to have a prevalence of 39.4% ahead of malignancy (27.2%), pneumonia (8%), empyema (5.2%), and TB (5.2%).<sup>[32]</sup> Confirming the diagnosis of CHF effusions can be achieved by measurement of serum and pleural fluid N-Terminal-Pro-B-Type natriuretic peptide (NT-proBNP) concentrations.<sup>[33]</sup> Yorgancıoğlu et al. studied NT-proBNP concentration in the serum and the pleural fluid of 45 patients. In 21 patients, pleural effusions were clinically attributed to heart failure; however, 14 of these 21 patients were classified as exudates by Light's criteria. The Median (25th to 75th percentiles) NT-proBNP levels of serum and pleural fluid due to congestive heart failure in these 21 patients were 4747 pg/mL (931-15754) and 4827 pg/mL (1290-12.430), while the median NT-proBNP levels of serum and pleural fluid related to non-cardiac reasons were 183 pg/mL (138-444) and 245 pg/mL (187-556) respectively ( $p < 0.001$  for both). The authors concluded that measurement of pleural fluid NT-proBNP is a smart approach and can reflect cardiac origin of effusions

better than Light's criteria. Another newer marker to identify patients with heart failure pleural effusions is the pleural fluid ischemia-modified albumin (PF-IMA). It was found to have a respective sensitivity and specificity of 90% and 80%, and a negative predictive value of 96% for CHF.<sup>[34]</sup>

Ascitic hydrothorax is commonly seen in patients with advanced liver cirrhosis. These immune-compromised patients can easily have a super-imposed bacterial infection of the effusion resulting in severe empyema.<sup>[35]</sup> Renal pathology is also known to cause usually transudative effusions. They can be encountered with or without either peritoneal or hemodialysis.<sup>[36]</sup>

### OTHER CAUSES FOR PLEURAL EFFUSIONS

A wealth of other pathologic conditions can cause pleural effusions in the Middle East. Some of them are more common than others. Venous thromboembolism is observed in both high risk patients and individuals with no obvious risk factors.<sup>[37]</sup> Pulmonary embolism can be complicated by either an exudative or transudative pleural effusion. Among other pulmonary conditions, chronic eosinophilic pneumonia can present itself with recurrent pleural effusion.<sup>[38]</sup>

Sarcoidosis can affect the respiratory system in various forms, one of them is pleurisy.<sup>[39]</sup> Rare infestations with amoeba, usually from a hepatic abscess, or complicated Hydatid cyst disease can present with peculiar empyema or hydropneumothorax.<sup>[40,41]</sup> Mechanical obstruction in the urinary tract can cause urinothorax<sup>[42]</sup>, while Imbalance between the production and absorption of cerebrospinal fluid following ventriculopleural shunt can end up in pleural effusion<sup>[43]</sup>. Other rare causes of fluid accumulation in the pleural space include: the ovarian hyperstimulation syndrome<sup>[44]</sup> and the Familial Yellow Nail Syndrome<sup>[45]</sup>.

### Conclusion

The spectrum of pleural disease is quite wide in the Middle East. While transudative effusions, especially from congestive cardiac failure remain prevalent, exudative ones seem to be more common with higher morbidity and mortality. Parapneumonic effusions usually carry a good outcome with therapeutic interventions. Pleural tuberculosis is encountered throughout the region with lengthy and sometimes difficult management. Human migration seems to increase its prevalence. Finally pleural malignancies are variable and generally carry a notoriously poor prognosis.

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**Cite this article as:** El-Sameed Y, Waness A, Mehta AC. Pleural Diseases in the Middle East: a 2013 review. *Int J Med Sci Public Health* 2014;3:116-120.  
**Source of Support:** Nil  
**Conflict of interest:** None declared