DIAGNOSTIC YIELD OF COMBINED EPIDEMIOLOGICAL AND RADIOLOGICAL DATA IN MALIGNANT PLEURAL MESOTHELIOMA: A PILOT STUDY

Zafar Iqbal , Mohammad Yousaf Khan , Jamshed Alam , Zia Ullah

[1-4] Department of Pulmonology, Lady Reading Hospital, Medical Teaching Institution, Peshawar – Pakistan.

Address for Correspondence:
Dr. Zafar Iqbal
Assistant Professor, Department of Pulmonology, Lady Reading Hospital, Medical Teaching Institution, Peshawar - Pakistan.
Email: drzafariqbalpulmo@gmail.com

Date Received: May 21, 2018
Date Revised: September 02, 2018
Date Accepted: September 09, 2018

ABSTRACT

Objective: To determine the diagnostic yield of epidemiological and radiological data in malignant pleural mesothelioma (MPM) patients.

Methodology: It was a survey of 56 patients between January 2014 to June 2017 who presented to chest clinic with gradual onset of pulmonary symptoms and had specific abnormal chest radiology. Computerized tomography (CT) guided biopsies were done and samples were sent for analysis for diagnostic yield of MPM. SPSS version 20 was used for statistical analysis.

Results: Among the study cases, 30 (53.6%) were male and mean age was 58.79 ±14.383 years). MPM was found in 28 (50%) cases. The diagnostic yield of epidemiological and radiological data showed sensitivity of (82.1%), specificity (14.3%), positive predictive value (48.9%) and negative predictive value (44.4%). The most commonly found marker was Cytokaratin which was present in 71.4% of the mesothelioma patients, followed by Calretinin (57.1%), and WT1 (50%).

Conclusion: Mesothelioma was found in half of the study participants. The diagnostic yield of epidemiological and radiological data showed increased sensitivity but low specificity regarding diagnosis of MPM.

Key Words: Asbestos, Mesothelioma, Pleural malignancies, Khyber Pakhtunkhwa, District Swabi

This article may be cited as: **Iqbal Z, Khan MY, Alam J, Ullah Z. Diagnostic yield of combined epidemiological and radiological data in malignant pleural mesothelioma: A pilot study. J Postgrad Med Inst 2018; 32(3): 236-41.**

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a very aggressive tumor, which arises from the mesothelial cells of the pleura. The most significant factor for the development of malignant mesothelioma is airborne asbestos fibers. MPM is no longer considered as un-common, as the use of asbestos is very much common these days. Asbestos is used as insulator against heat, fires and corrosions. It is mainly used in material for home construction, cement, ceiling, tiles, gas kits, car bracers, jewelry and even in toys. Due to the diverse use and exposure of asbestos results in high incidence of mesothelioma in Pakistan, particularly in Khyber Pakhtunkhwa (KPK)[1]. Besides occupational history, environmental exposure to asbestos fibers commonly found in northern districts of the province of KPK, is presumed to be the main causative agent for MPM. Though human beings have been using asbestos for ages[2,3], but the potentially carcinogenic airborne asbestos fibers in the environment have not come under consideration till recent past[4,5].

The major rock belts containing rich amount of asbestos are located in KPK and adjacent Federally Administered Tribal Areas (FATA). Overall in Pakistan, about 90% of asbestos is found in KP region. Asbestos fibers find their way into the environment and become airborne during the process of quarrying, cutting and freeing it from rocks by blowing and crushing[6]. The concentration of respirable airborne fiber in the mining area in Pakistan are much higher than the permissible limits[7]. It has been reported in a study by Jehan[8] that asbestos fibers in surrounding field was more than 100 times than its permissible amount.

Unfortunately, in KPK, the workers are not aware of the concept of occupational safety and industrial hygiene, mainly because of poverty[9]. These people are working in marble/mining rocks using shovels for extraction and using bare hands for the spread of asbestos for drying, without considering the possible release of associated fibrous asbestos in the environment. It was observed in a study by Jehan et al[9] that people working there or nearby residents have a lot of medical issues

like skin allergies, chronic bronchitis, pleural thickening and calcified pleural plaques on radiology[10].

The developed countries have already banned the use of asbestos due its proven health hazards, but the developing countries like Pakistan is still facing the threat from this fatal dust i.e. micro-fibers of asbestos. Because of this un-regulated asbestos business, unfortunately a significant increase in number of mesothelioma patients in KPK is expected[11].

When this environmental asbestos fibers go into the respiratory tract, it pierces its parenchyma, ends up in the pleura, inducing cytotoxicity, DNA changes and chronic inflammatory response resulting in abnormal mitosis, which leads to development of mesothelioma[12,13]. Clinico-radiological features play an important role in the diagnostic process as the histopathological diagnosis is often difficult due to variety of reasons including the nodular nature of disease, difficulty in selection of histochemical stain and the associated pleural effusion.

CT and chest X-ray both play an important role in the diagnosis. The most common mesothelioma findings are pleural plaques, nodular pleural thickening and concentric pleural thickening, resulting in encasement of the lung parenchyma. This research was conducted as a pilot study to assess the role of combined epidemiological and radiological data in the diagnosis of mesothelioma. We assessed the suspected patients of mesothelioma belonging to District Swabi. This study will help in creating awareness among clinicians regarding mesothelioma development due to environmental asbestos exposure and guidance regarding diagnostic modality for MPM.

METHODOLOGY

This study was conducted in chest clinic in District Swabi, KPK, Pakistan, between January 2014 to June 2017. All the patients enrolled in this study belonged to District Swabi who presented to chest clinic with gradual onset of pulmonary symptoms such as chest pain, dyspnea, cough. They were assessed with chest X-ray and CT thorax for findings consistent with mesothelioma (encasement, nodularity and pleural thickening on chest X-ray and CT thorax). Chest X-ray was considered positive when there was unilateral, concentric, plaque like or nodular pleural thickening. Positive CT thorax was defined when there was concentric pleural thickening or nodular pleural thickening or pleural thickening more than 1cm and or involvement of mediastinal pleura (Figure 1). Epidemiological data was definedIt as the data collected from patients from District Swabi to find out distribution (frequency, pattern) and determinants (causes, risk factors) of mesothelioma especially asbestos exposure. Ultrasound chest was done to exclude large effusion; and patients not fit for CT guided biopsy because of desaturation were excluded from study.

The enrolled patients were then referred for image guided biopsy to an experience radiologist and the specimens were sent to Shaukat Khanum Memorial Cancer and Research Hospital Laboratory for histpathology and immunohistochemial staining. All the patients were biopsied after a verbal and written informed consent. Three to four pieces of biopsies were taken, using tru cut biopsy needle. Two percent (2%) lignocain was used as local anesthetic.

Intravenous midazolam and/or tramadol was used in excessively apprehensive cases. No serious complications were observed except for mild localized pain and occasional faintness in over apprehensive patients. None of the patients needed an invasive intervention to treat a complication of the procedure.

Data were collected, coded and entered to a computer before being analyzed using the software, SPSS version 20. Qualitative data (gender, radiological findings, presence of mesothelioma) were presented as frequency and percentage; while quantitative data (age) were presented as means and standard deviation. Comparisons of qualitative data were performed using Chi-squared test while validation tests were applied for determining the diagnostic yield. P-values of <0.05 were considered the cut off point for the level of significance.

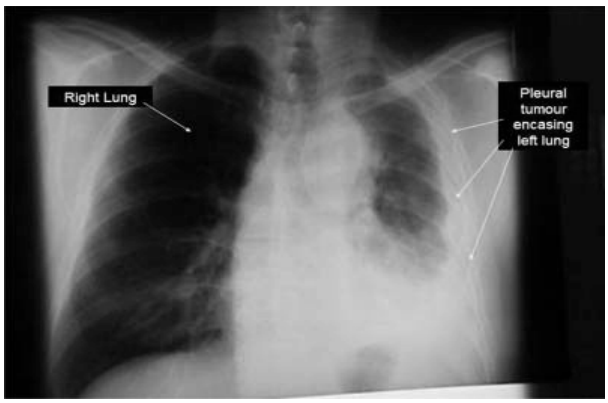
RESULTS

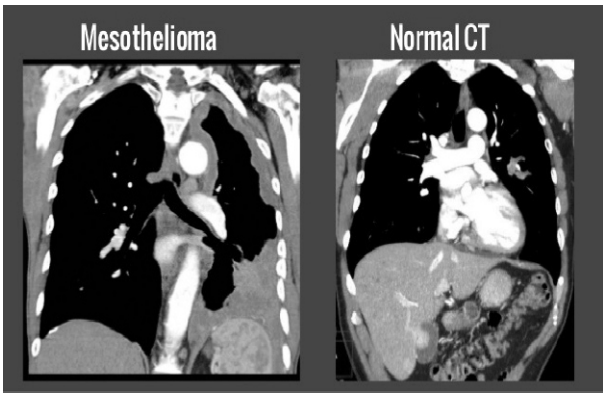
The common findings on X-ray and CT thorax were unilateral concentric nodular pleural thickening with pleural plaques in 83.9% of the total cases. There was no significant statistical difference between chest X-ray and CT thorax findings. However, on CT thorax, mediastinal pleura was also involved in 46.4% which is pathognomonic of mesothelioma (Table 1).

Among total cases, 30 (53.6%) were male and 26 (46.4%) were female whereas majority of the patients with mesothelioma were males (64.2%, Table 2). Minimum age of the patients was 32 whereas maximum age was 80 and mean age was 58.79 ±14.383 years. Most (78.6%) were older than 50 years. Age distribution is shown in Table 3. Among study patients, 26 (46.4%) were house wives, 18 (32.2%) farmers, 10 (7.8%) shopkeepers and 2(3.5%) were school teachers by occupation. There was no occupational exposure to asbestosis in any case and only 6 (10.7%) had history of smoking. The main presenting complaints were chest pain (89.2%), followed by cough (71.4%), shortness of breath (35.7%) and fever 8 (14.2%) cases.

Mesothelioma was found in 28 (50%) of the study cases, whereas other 28 cases (50%) were negative for mesothelioma (Table 4). The most common marker was

Figure 1: chest X-ray showing pleural tumor encasing left lung and irregular concentric pleural thickening on CT Thorax





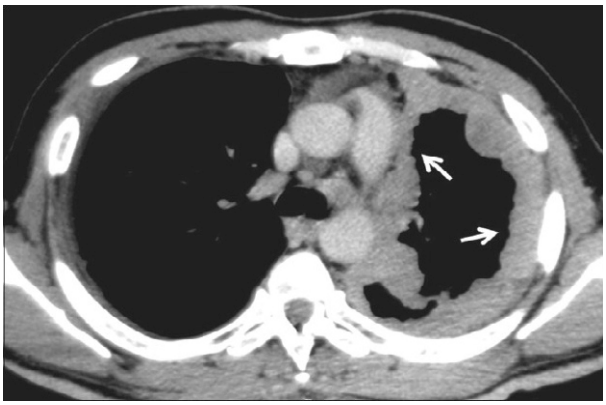


Table 1: Comparison between CT thorax and chest X-ray (n=56)

Findings	X-Ray		CT Thorax	
	Frequency	Percentage	Frequency	Percentage
Nodular Pleural Thickening	47	83.9	47	83.9
Concentric Pleural Thickening	40	71.4	40	71.4
Pleural Plaques	44	78.6	44	78.6
Involvement of Mediastincal Pleura	7	12.5	26	46.4

Table 2: Gender of the study cases (n=56)

Gender	All Cases		Mesothelioma Cases		P Value
	Frequency	Percentage	Frequency	Percentage	
Male	30	53.6	18	64.2	>0.05
Female	26	46.4	10	35.8	
Total	56	100	28	100	

Table 3: Age distribution of Mesothelioma patients (n=28)

Age group (Years)	Frequency	Percentage
30 - 40	01	3.5
40 - 50	03	10.7
Above 50	24	85.7
Total	28	100

Table 4: Histopathological diagnosis (n=56)

Findings	Frequency	Percentage
Mesothelioma	28	50
Other Malignancy	20	35.7
Metastatic Adenocarcinoma	10	
Small Cell Lung Carcinoma	2	
Poorly Differentiated Adenocarcinoma	6	
Moderately Differentiated Adenocarcinoma	2	
Negative for Malignancy	08	14.3
Non -diagnostic Biopsy	2	
Solatiry Fibrous Tumor	2	
Anthracosis	1	
Chronic Pyogenic Inflammatory Infection	3	
Total	56	100

Table 5: Presence of markers in mesothelioma cases (n=28)

Markers	Frequency	Percentage
Cytokeratin	20	71.4
Calretinin	16	57.1
WT1	14	50
D240	10	35.7
HBME	10	35.7

Table 6: Diagnostic yield compared to histopathological diagnosis of MPM (n=56)

Tests Report	Mesothelioma		Total
	Present	Not Present	
Positive	23	24	47
Negative	05	04	09
Total	28	28	56

Cytokaratin which was present in 71.4% of cases followed by Calretinin in 57.1% cases (Table 5).

Diagnostic yield of MPM revealed sensitivity as (23/28x100=82.1%); specificity (04/28x100)=14.3%; positive predictive value (23/47x100)=48.9%; and negative predictive value (04/09x100)=44.4% (Table 6).

DISCUSSION

Many studies have mentioned the presence of asbestos reserves in the north-west of Pakistan[14-17]. A study was conducted in Mohmand Agency and it was found that there is vast reserves of chrysotile, tremolite and anthophyllite asbestos deposits. It was noted that the physical size of asbestos fibers in the area was well within the potentially carcinogenic asbestos-fiber size (i.e. within the range of <3.5 micrometer in diameter and >5 micrometer in length). The amount of the airborne asbestos fibers was more than 100-times the permissible level of 0.1f/cc[18].

A cause and effect relation between environmental asbestos exposure and mesothelioma in the FATA and the KPK province of Pakistan was first established in the 1990s and was published in the year 2001[19]. The histological diagnosis of mesothelioma reported in that study was questioned because immunohistochemical (IHC) markers were not applied. Biopsy specimens obtained via closed pleural biopsies are small and pose difficulty in reaching a definitive diagnosis of mesothelioma. Moreover, the three histological types of mesothelioma; namely epithelioid, sarcomatoid and mixed variety can resemble other malignancies. This issue can be resolved by simultaneously applying positive IHC-markers for confirmation of mesothelioma and negative IHC-markers for ruling out other malignancies[20-24]. In our study, various IHC-markers were applied to the histopatholo-

gy specimens. Thus a definitive diagnosis of malignant mesothelioma was made and relationship between environmental asbestos exposure and mesothelioma was shown.

Swabi, one of the district in KPK, in North West of Pakistan, has the highest prevalence of MPM[14] and environmental exposure is thought to be the cause of the disease. Due to this reason, it can affect the younger age group as well without any occupational exposure as it is evident in our study (about 15% of our patients were less than 50 years old). Usually mesothelioma occurs in late ages as evident from our study and the study done by Jehan et al[25]. Usually after exposure it takes 20-30 years to develop mesotherlioma, because of long latent period between onset and symptoms[26]. However, in this locality mainly its seems to be environmental exposure in childhood. Moreover, the females who worked mostly at home developed mesothelioma as well. So from our study it is quite evident that there is something in the environment and the question arises here whether something is present at home or is airborne or genetic in origin. Of note, the males were 88% farmers by occupation and this raises question if our farms are rich in asbestos as mentioned by Jehan et al[25]. But if we look at our females cohort they were 100% housewives.

One explanation would be that as they live near farms, they could potentially get asbestos exposure and the second possibility will be the presence of something household or which they share indoor. Because of the limited resources and interest we are still not confident that whether this is something in the gene, in the farms nearby at homes or airborne from nearby mining industry. For this further work need to be done.

Malignant pleural mesothelioma was found in 50% of our patients, which is quite significant. Interestingly it was followed by adenocarcinoma (32%) which could potentially be peripheral lung tumor involving pleura. Regarding diagnostic yield, the sensitivity was high (82.1%), though the specificity was very low (14.3%). Although epidemiological and radiological data can not establish the diagnosis of MPM, but these may provide substantial evidence to suggest MPM. Therefore, anyone from the mention endemic area need to be suspected for MPM with typical radiological pattern on chest X-ray or CT thorax without pleural effusion, regardless of the occupation or history of asbestos exposure[28].

LIMITATIONS

Critic could ask potentially the deficiency in history regarding the use of asbestos in buildings, houses near the mining industries, information about the farms nearby and mining industries and family history of the mesothelioma. As this study was conducted in a peripheral primary care setting clinics, there was no dedicated radiologists available onsite. And we feel that we could possibly bring down the number of non-mesothelioma cases to increase the sensitivity of our study for diagnosing MPM if these were collaborated with tertiary care radiology team.

CONCLUSION

Mesothelioma was found in half of the study participants. It was significantly more common in males aged 50 years and above. The most commonly found biomarkers was Cytokaratin followed by Calretinin. The diagnostic yield of epidemiological and radiological data showed increased sensitivity but low specificity.

RECOMMENDATIONS

Malignant pleural Mesothelioma is a common and rapidly fatal and aggressive tumor. The diagnosis is often delayed, due to a long latent period between onset and symptoms and the common, nonspecific clinical presentation. There should be a considerably high level of index of suspicion in mind, when an irregular pleural thickening or encasement on X-ray chest or CT Thorax is seen. High prevalence of the MPM in the district Swabi warrants further investigation and any abnormal radiology should be promptly investigated for MPM.

REFERENCES

1. Donoghue AM. Occupational Health Hazards in Mining in Pakistan: An Overview. Occup Med (Lond) 2004; 54:283-9.
2. Dilek Y, Newcomb S. Ophiolite Concept and the Evolution of Geological Thought. Geolog Soc Am 2003; 141:390-1.
3. Rapp GR. Archaeomineralogy. Berlin Springer; 2009.
4. International Agency for Research on Cancer. Asbestos (Chrysolite, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite). Int Agen Res Cancer 2012: 147–67.
5. Jehan, N, Ahmad I. Petrochemistry of asbestos bearing rocks from Skhakot-Qila Ultramafic Complex, northern Pakistan. J Himal Earth Sci 2006; 39:75-83.
6. Hamidullah, S. Asbestos occurrences in Mohmand Agency: Genesis, economics and related health hazards: Geological Bulletin, Univ Pesh 1984; 17:69-73.
7. Iftikhar S, Ali M, Nergis Y. Risks and Hazards Study of Asbestos in Pakistan. Int J Econ Environ Geol 2015; 6:25-8.
8. Jehan N. Sustainable management of mineral resources with special reference to asbestos and sil-

ica in Northern Pakistan 2004. Nation Cent Excell Geol Univ Pesh 2004:1-219.

9. Jehan K, Khan AN. Spheroidal asbestos from Qila, Charsadda Tehsil. Pakistan. J Sci Indus Res 1963; 16:266-7.
10. Ronnegard N. Lungrontgenfynd och asbestexposition balnd mellansvenska gruvarbetare (Pulmonary X-Ray findings and asbestos exposure in miners from central Sweden). Solna: Arbetarskyddsstyrelsen, 17. (Projekt AD 238/83. In Swedish) 1985.
11. Leong, SL, Zainudin R, Kazan-Allen L. Robinston BW. Asbestos in Asia. Resirology 2015; 20:548-55.
12. Jaurand MC, Fleury-Feith J. Pathogenis of malignant pleural mesothelioma. Respirology 2005; 10:2-8
13. Jean D, Daubriac J, Le Pimpec-Barthes F, Galaleau-Salle F, Jaurand MC. Molecular changes in mesotherlioma with an impact on prognosis and treatment. Arch Pathol Lab Med 2012; 136:277-93.
14. Qaisar MA, Ali K, Khan AH. Mineralogy of asbestos from north-west Pakistan. J Sci Indus Res 1967; 10:116-20.
15. Rafiq M, Shah MT, Ahmad I. Note on tremolite zone from the extension of Shkakote-Qila Ultramafic complex in Utmankhel, Mohmand Agency. Geol. Bull. Univ. Peshawar 1984; 17:178-9.
16. Rafiq M. Extension of Shkakot Qila ultramafic complex in Utman khel, Mohmand Agency, NWFP, Pakitan. Geol Bull Univ Pesh 1984; 17:53-9.
17. Jehan N. Asbestos risks: occupational and paraoccupational health status in Pakistan. Glob Asbes conf; 2004.
18. Jehan N, Ahmed I. Fibrogenic and carcinogenic characteristics of Asbestos occurring in Mohmand Agency. Northern Pakistan: Geol Bull Univ Peshawar; 2005.
19. Javaid A, Ziaullah. Malignant Mesothelioma in NWFP, Pakistan. Pak J Chest Med 2001; 7:3-10.
20. Husain AN, Colby TV, Ordóñez NG, Krausz T, Borczuk A, Cagle PT et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arc Pathol Lab Med 2009; 133:1317-31.
21. Ordóñez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003; 27:1031-51.
22. Ordóñez NG. What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma? A review and update. Hum Pathol 2007; 38:1-6.
23. King JE, Thatcher N, Pickering CA, Hasleton PS. Sensitivity and specificity of immunohistochemical markers used in the diagnosis of epithelioid mesothelioma: a detailed systematic analysis using published data. Histopathology 2006; 48:223-32.
24. Lucas DR, Pass HI, Madan SK, Adsay NV, Wali A, Tabaczka P, Lonardo F. Sarcomatoid mesothelioma and its histological mimics: a comparative immunohistochemical study. Histopathology 2003; 42:270-9.
25. Jehan N, Ahmad I. Occurance of tremolitic asbestos in Nowshera Formation Ghundai Trako, district Swabi, Norht Pakistan. J Himal Earth Sci 2007; 40:67-9.
26. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer. 1982; 45:124.
27. Reid A, De Klerk NH, Magnani C, Ferrante D, Berry G, Musk AW, Merler E. Mesothelioma risk after 40 years since first exposure to asbestos: a pooled analysis. Thorax 2014; 69:843-50.
28. World Bank. Good Practice note: Asbestos: Occupational and community health issues. Trad Uni Cong Philip; 2010.

CONTRIBUTORS

ZI conceived the idea, planned the study and drafted the manuscript. JA and ZU helped acquisition of data and did statistical analysis. MYK critically revised the manuscript and supervised the study. All authors contributed significantly to the submitted manuscript.