Pleural mesothelioma in paraoccupational, environmental and occupational patients exposed to asbestos

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RESUMEN

Objetivo: estudiar las características del mesotelioma pleural maligno en pacientes con exposición paraocupacional, ambiental y ocupacional a asbesto, de 2000 a 2004.

Métodos: estudio transversal de 3700 casos de cáncer pulmonar. Las variables fueron edad, sexo, tabaquismo, variedad histopatológica de mesotelioma, diseminación, citohistoquímica, letalidad y capacidad pulmonar total. Se usó Anova para identificar diferencias entre los grupos.

Resultados: se diagnosticaron 21 casos: 20 hombres y una mujer; 19, 33 y 48 % por exposición ocupacional, paraocupacional y ambiental. La edad de detección fue de 50, 55 y 64 años, respectivamente. En 19 pacientes el tumor se diseminó por contigüidad. En todos el diagnóstico se confirmó por citohistoquímica. El tiempo de latencia fue de 40, 34.5 y más de 40 años para el cáncer ocupacional, paraocupacional y ambiental. La supervivencia fue de 5, 10 y 16 meses, respectivamente. La capacidad pulmonar total estuvo disminuida en todos.

Conclusiones: la incidencia del mesotelioma pleural fue baja; predominó en el sexo masculino y ante exposición ocupacional y paraocupacional. La letalidad es alta a corto plazo.

SUMMARY

Objective: to identify the characteristics of pleural mesothelioma in patients exposed to asbestos.

Methods: a transversal study in 3700 cases of lung cancer was conducted. There were identified 21 cases with mesothelioma. Age, gender, smoking history, cancer development, dissemination, cytohistochemistry, lethality and total lung capacity were studied. ANOVA test was used.

Results: the incidence was of 0.45/100,000 patients. Four (19 %) corresponded to occupational exposure (OE), seven (33 %) para-occupational (PE) and ten (48 %) environmental (EE). The mean age at detection was 50 years for PE, 55 years for EE and 64 years for OE. Twenty cases were male. Thirteen patients (62 %) were active cigarette smokers. The latency time in PE mesothelioma was 34.5 years, in OE 40 years, and in EE more than 40 years. In 19 (90 %) cases the tumor was disseminated. Diagnosis was confirmed by cytohistochemistry. Malignant mesothelioma was reported in 19 (90 %) cases. The survival period was 5 months for OE patients, 10 in PE and 16 in EE.

Conclusions: there is a low incidence of malignant mesothelioma in our population. Male was the predominant group. Occupational and paraoccupational exposure predominated in patients.

Palabras clave
mesotelioma
enfermedades pleurales
enfermedades profesionales
asbesto

Key words
mesothelioma
pleural diseases
occupational diseases
asbestos

Introduction

Asbestos is a material that has been used for more than 2000 years. It has more than three thousand uses. The chemical composition, fiber and crystalline structure of the amianto contribute to asbestos exceptional properties in numerous industrial applications such as: non-combustion, thermo-resistance, and low thermal conductivity, resistance to chemical substances acid or alkaline, microorganisms and erosion. It has also been reported in previous articles that asbestos has persisted in the environment for up to 50 years.[1-6]

Statistics in Mexico showed that in 2003; 804,389 enterprises were registered in the *Instituto Mexicano del Seguro Social* (IMSS), in which 7,811 work-related diseases were reported out of 12,088,468 medically insured persons working with occupational hazards. 37 % of them in the country are bronco-pulmonary origin:[7] 10 % are pneumoconiosis, 4 % chemical bron-

chitis, 3 % pneumoconiosis caused by coal inhalation and 0.02% malignant pleural mesothelioma.

The main sources of occupational exposure (OE) related to asbestos at work are: open cast mines, deep mines and transformation industries, mainly the fibrocement manufacturer, boilers, pipes, production of abrasive materials, automobile brake linings, construction components for buildings insulation, heat resistant bricks, cleaning materials, maintenance of ventilation ducts, fiber and dusts deposits. Paraoccupational exposure (PE) includes the workers who are not exposed daily, but intermittent exposure, inhabitants who live in the proximity of the factories that manufacture asbestos, inhabitants near the mines, maintenance workers of power stations, plumbers, milling plants and garbage dumps. Environmental exposure (EE) corresponds to the inhabitants of large polluted cities. This exposure is not enough to produce asbestosis, mesothelioma nor pulmonary cancer.[8,9]

In 1972 Selikoff[10] reported that the possibility of acquiring the disease depends on the duration, amount and level of exposure to fibers. With greater exposition, higher risk for acquiring bronchial carcinoma. At lesser but longer duration period of exposure, the greater possibility of developing malignant pleural mesothelioma. There are other factors that increase the risk of acquiring asbestosis: history of bronchopulmonary diseases, individual susceptibility, lifestyle, smoking and inadequate management of waste material, work clothing and asbestos fibers.

Xue-lei Pan *et al*.[11] reported in 2005 a case control study concerning environmental exposure of inhabitants with residence in the proximity of naturally occurring asbestos (we called paraoccupational exposure in our paper), and performed an hypothesis on the highest risk of developing malignant pleural mesothelioma, which diminishes in approximately 6.3 % for every 10 km farther from the nearest asbestos source. He classifies the exposure to asbestos into three groups: low, medium and high. Selikoff[10] identified occupational, paraoccupational and environmental exposure in a similar way.

Inhaled fibers can reach the respiratory bronchiole and the pulmonary alveoli where asbestos causes pneumoconiosis. The pulmonary fibrosis related to asbestos pneumoconiosis, evolves anywhere from 2 to 5 years to death. Meanwhile the quality of life deteriorates rapidly. This condition can be accompanied by unilateral pleural effusion which sometimes is asymptomatic and disappears spontaneously. The malignant mesothelioma can also be produced by inhalation of asbestos fibers with a latency period of 20 years or more. This is a primary pleural tumor which has a rate of incidence in the general population of less than 1 per 100,000 inhabitants; it can also be developed rarely in peritoneum and pericardium.[8]

Morgan *et al.*[12] mention that inhalation and deposit of asbestos fibers in the respiratory track can produce the following pathologies: asbestosis with the consequent pulmonary fibrosis, bilateral widespread, bronchogenic carcinoma in persons who have been diagnosed with asbestosis, malignant pleural mesothelioma, peritoneal mesothelioma, pleural effusion caused by pleural thickening and pleural plaques which can be calcified due to asbestos.

A linear relationship has been demonstrated between dose and risk; the worker who has been intensively exposed to asbestos develops asbestosis, the one who has been less exposed will develop bronchogenic carcinoma and the one with the lower exposed concentration will develop malignant pleural mesothelioma after 20 or 40 years of latency. In other words the type of exposure could be: occupational, paraoccupational and environmental.[10,13,14]

The first description of pleural mesothelioma in asbestos workers was made by Wyers[15] in Glasgow in 1946. In 1960, Wagner[16,17] described the association between the exposure to asbestos and the production of malignant mesothelioma, in workers exposed to asbestos as well as residents living near the asbestos mines in South Africa. Since then, the number of reported cases in the international medical literature regarding pleural tumors and mesothelioma related to occupational exposure to asbestos has increased constantly.[8,9,12-15]

In London, it was calculated that by the year 2000, the mortality due to mesothelioma in men who worked with asbestos in the textile industry before 1964; would be 7 to 11 % of total mortality in males.[16,18] Some countries reported that in 15 % of malignant pleural mesothelioma cases, there was no relation with environmental or industrial exposure. Although in Holland, Zielhuis *et al.* reported that in 100 % of the cases in which they studied, the exposure to asbestos was demonstrated.[14-20]

Méndez *et al.*[20] described in 1982 the first case of pleural mesothelioma in Mexico. It was a worker who was exposed to chrisolite and crocidolite during a period of 16 years. This case was included in the Oncology Overview of 1986.* In 1992, the same authors published ten cases related to occupational exposure to asbestos: seven with pleural mesothelioma, one with epidermoid bronchogenic carcinoma and two with adenocarcinoma.[21]

Berry, during the period 1979 to 1990, reported the results of the evaluation of paraoccupational exposure, in persons that lived in Manville, New Jersey; where the majority of factories that processed asbes-

*Méndez V, Maldonado T, Stanislawski E, Mendoza U. Malignant mesothelioma in an asbestos worker. Oncology Overview 1986:20.

tos in North-America were located. 636 cases of malignant pleural mesothelioma were found in males and 96 in females per one million inhabitants. This figure is 25 times more than the expected average for cancer in the general population in the United States, who apparently were not exposed to asbestos.[22]

Kjaergaard[23] during the period 1943 to 1992 published that the average survival rate of malignant pleural mesothelioma is 6.9 months for males and 7.8 months for females. Boutin[24] indicates that no one single effective treatment exists to treat this tumor and the survival period is 12 to 17 months following the diagnosis.

In Australia, a country which reports the highest incidence of mesothelioma in the world; 858 cases were studied from 1980 to 1985. Occupational exposure to asbestos was verified in 57 % of the cases. 137 (28 %) of them corresponded to industries where the main raw material was asbestos, followed by 114 (23 %) in shipbuilding, repair and demolition, 69 (14 %) in the building industry, and 47 (10 %) in the railway locomotive construction and maintenance industry.[25]

Magnani *et al.* in a case-control study carried out in six regions of Italy, Spain and Switzerland, reported 215 histological confirmed cases of malignant pleural mesothelioma and 448 controls.[26]

A panel of industrial hygienists carried out the environmental evaluation to quantify separately the occupational, paraoccupational and environmental exposure to asbestos. 53 cases and 232 controls without evidence of occupational exposure had paraoccupational exposure to asbestos. They conclude that people who live between 2000 and 5000 meters from the asbestos mines or 500 meters from the industries that processes asbestos, have an increased risk for developing malignant pleural mesothelioma. They suggest that the exposure to a low dose of asbestos, increases the risk of developing malignant pleural mesothelioma.[26]

Koskinen *et al.* in 2002 mentioned that the greater the amount of fibrosis, the highest possibility of developing bronchogenic carcinoma, which is present more often in insulation workers who use spray-in techniques. This information has been ratified by other authors, reporting that mesothelioma can be produced with low levels of exposure to asbestos.[27]

Methods

A transversal and retrolective study was carried out. The gathering of data was made from January 2nd to November 30th 2004. The cases were selected according to the following inclusion criteria: Both sexes, patients who received medical attention in the reference oncologic hospital from 2000 to 2004, diagnosed with lung cancer. All varieties of malignant pleural mesothelioma were included, diagnosed by histological and cytochemestry studies, and all the cases should have a chest x-ray, high resolution computed tomography, spirometry and corporeal plethysmography. The laboral history was requested related to the exposure to asbestos and was classified as the following: Occupational in those workers in direct contact with asbestos, paraoccupational in subjects who lived or worked within 800 meters from an industry that processes asbestos, and environmental in those subjects who did not have a history of occupational or paraoccupational exposure. In each one of the cases, the exposure characteristics were described in detail using a clinical format performed specifically for this study.

Due to the low incidence and prevalence of this disease in the world, this study included 100 % of the cases diagnosed with malignant pleural mesothelioma during the period 2000 and 2004.

Statistical management was carried out by means of central tendency and dispersion measurements; to identify differences among study groups, we applied analysis of variance test with Tukey correction.

Results

Twenty one cases of malignant pleural mesothelioma were diagnosed (0.56 %) that full field the inclusion criteria. Out of the total of 3,700 cases of lung cancer registered in a Reference Oncologic Hospital, from 2000 to 2004 with a rate of 0.9/100,000. Considering that the IMSS insured population corresponds to approximately 2,271,668 workers; the incidence was calculated at 0.46/100,000 patients. Of these patients, four (19 %) belonged to OE, seven (33 %) had PE and ten (48 %) EE. There were 20 males (95 %), and one (5 %) female which belonged to the OE group. The mean age was 63.6 ± 6.3 years for the OE, 52.75 ± 9.32 years for the PE and 53.13 ± 14.88 years for the EE (table I).

There were 13 (62 %) patients with a positive history of smoking. Concerning the smokers, one (4.7 %) belonged to the OE, four (19 %) to the PE and eight (37.6 %) to the EE group. According to the three aforementioned groups; the first one had a media of 14.67 ± 21.94 years smoking, the second group had 13.5 ± 23.01 years, and the third one had 25.75 ± 23.43 years; with a p value < 0.05 for the EE group. With respect to the number of cigarettes

per day, the EE group had the largest amount with a media of 11.25, followed by the OE with 6.67, and finally the PE with 3.25 cigarettes smoked per day.

The latency mean time since the first symptom began until the tumor was diagnosed was 8.25 months for the PE, followed by the cases of EE with 6.75 months and finally the OE with five months.

The tumor lethality was higher in the patients with OE with a mean of 15 months, followed by the patients with PE with 11.67 months and finally the patients with EE with 8 months ($p < 0.05$). The latency time regarding the development of the tumor was greater in the OE group with a mean of 40 years, followed by the PE which was 34.5 years, and in the EE group, it was not possible to obtain the exact date when the exposure began. However, it can be inferred that the exposure occurs at an early age ($p < 0.08$).

The spirometry showed a different grade of decrease in the forced vital capacity (FVC) and the slow vital capacity (SVC), and a positive Tiffeneau index over +6. The corporeal plethysmography confirmed the decreased total pulmonary capacity (TLC). With regard to the groups of exposure; the mean TLC was greater in the EE group with a measurement of 74 %, followed by the OE with 75 % and lastly, the PE with a mean of 59 %. The mean of the three groups was 69.9 % ($p < 0.05$).

A significant fact in the cases studied was the tumor spread by direct extension, which was present in 19 (90 %) of the 21 cases.

Metastases were present in 14 (67%) cases, of these, four (20 %) belonged to the OE, three (21 %) to the PE, and seven (50 %) to the EE group. This parameter is not useful in evaluating the exposure, but to recognize how advanced the stage of the tumor is. In 13 (62 %) patients, the tumor was located in the right hemithorax and in eight (38 %) in the left (table I).

Table I
Clinical and occupational characteristics of 21 workers with mesothelioma according to exposure type from 2000 to 2004

	n	%	*p*
Gender			
Male	20	95	
Female	1	5	
Type of exposure			
Occupational	4	19	
Paraoccupational	7	33	
Environmental	10	48	< 0.05
Metastases (14 cases)			
Occupational	4	29	
Paraoccupational	3	21	
Environmental	7	50	
Hystochemical variety			
Deciduoid malignant mesothelioma	2	9	
Epithelial malignant mesothelioma	19	91	
Lethality (months)			
Occupational	15	–	
Paraoccupational	12	–	
Environmental	8	–	< 0.05
Average age of patients when the tumor appeared (years)		–	
Occupational	63.67 ± 6.3	–	
Paraoccupational	52.75 ± 9.72	–	
Environmental	53.13 ± 14.88		
Latency time (years)			
Occupational	40.0	–	
Paraoccupational	34.5	–	
Environmental	40.0	–	< 0.08
Total pulmonary capacity (%)			
Occupational	75	–	
Paraoccupational	59	–	
Environmental	74	–	
Tumor spread			
Direct contiguous extension	19	90	
Yes No	2	10	< 0.05

Source: Compilation information registry 2000-2004

Discussion

Of the 21 cases studied with mesothelioma, 20 (95 %) were males, in accordance with the international literature, given that men are the predominant working group in the asbestos manufacturing industries. However, the mesothelioma presented in both sexes in the PE and EE population.

The malignant pleural mesothelioma was diagnosed at an average age of 53 years in the PE group; probably explained by the subjects being exposed to asbestos at earlier, given that they lived since childhood near the industries that process raw asbestos material. This was reported in a specific case which was included in the population studied. This patient was exposed to asbestos since the age of 3 years and lived less than a mile from an asbestos processing plant. In the EE exposure group, the mesothelioma

was diagnosed at an average age of 55, but the time of exposure was unavailable in these cases. Finally, in the OE group, the tumor was developed at an average age of 64, given that the exposure starts at least at 18 years of age, prolonging the latency time when the tumor appears. This data coincides with the international literature.

With regard to smoking habits; 8 workers were smokers. The EE group, had the longer period of smoking duration with a mean of 26 years with an average of 11 cigarettes per day, followed by the OE group with a mean of 15 years smoking with an average of 6.67 cigarettes a day. Finally, the PE group, with 13 years means smoking and 3 cigarettes per day. Despite the fact that smoking is not associated with the development of malignant pleural mesothelioma, it has been proven to be a promoter for bronchogenic carcinoma and the asbestos as an initiator, so their effects are potentiated for the development of bronchogenic carcinoma, but it does not have any influence on the development of the mesothelioma. According to the exposure time to asbestos and its varieties established by Selikoff, it was observed that in the OE group the mean time was 19 years and 10 years in the PE group. It is mentioned that the most important fact in order to develop the tumor is the latency period which is a very long period of time consisting of 20 years or more.

We reported a case that had a latency time of more than 50 years.[20] In this paper, the latency time in the exposed subjects to asbestos in the OE group was 40 years and in the paraoccupational group, it was 34 years. It was not possible to evaluate the EE.

With respect to the evolution time, the mean was 7 months. There are no reports in the literature which mention how much time elapses between the onset of the symptoms and the diagnosis. The diagnosis should be made early to establish the most appropriate therapeutic scheme, taking in account the variety of the tumor. However, the prognosis is poor with short-term survival. Epidemiological monitoring is vitally important and should be applied by a multidisciplinary team of specialists in medicine, industrial hygiene and environmental engineering control; identifying the varieties of asbestos to which the general population are exposed. The spirometry and corporeal plethysmography confirm the diagnosis of restrictive pattern, secondary to constrictive pleural thickening produced by the malignant pleural mesothelioma. This restriction affects the mechanical properties of the lung producing a decrease in pulmonary distensibility (compliance) and increasing the pulmonary elastic retraction (elastance). These alterations were shown in the three groups studied. According to the histological variety of the tumor, the epithelial type predominates as it has been reported in the medical literature. The tumor spread by direct contiguous extension in 19 (90 %) cases. However, metastases produced by lymphohematogenous dissemination were present in 14 (67 %) cases.

The tumor mortality was higher in the OE cases with a survival period of only 5 months, followed by the PE with a 10 month period, and the best survival rate occurred in the EE cases with 16 months. We consider that this fact can be explained by the tumor stage at the moment of the diagnosis, the histological variety, the patient's general condition at the beginning of the cancer and the genetic susceptibility. The survival rate reported in the literature for mesothelioma is between five to seven months; in our study, it was 10.3 months.

In the occupational health field, the PE (corresponds to moderate exposure in the Xue-Lei-Pan classification).

Up until now, not one author has reported that the EE would be enough to produce mesothelioma. The chief of the industrial medical service should receive training in occupational bronchopulmonary diseases and specifically in the ones produced by asbestos as well as its varieties, with the objective to establish the preventive disease programs through: conferences directed at industrial medical personnel and laborers concerning the topics of hygiene education, adequate management of industrial waste material, work clothing and asbestos fibers. Furthermore, industries should count with the technical resources. All these measures have the purpose of implementing preventive bronchogenic carcinoma programs and improving the work and scientific performance.

Conclusions

The pleural malignant mesothelioma occurs in subjects with OE and PE to asbestos with a latency period of more than 20 years, but never in patients with EE. In spite of our findings, we concluded that the patients, who developed mesothelioma with apparently environmental exposure, may have had PE to asbestos which had gone unnoticed. The prevention has a key importance in workers exposed to asbestos. Recognizing that asbestos is a very dangerous material, its use should be prohibited all over the world or at least its management should be strictly regulated.

References

1. Energy, Mines and Resources Canada. El amianto. Ottawa, Canada. Energy, Mines and Resources Canada; 1986.
2. Parkes WR. Occupational lung disorders. London: Butterworth; 1982. p. 134-174.
3. Méndez M, Maldonado T. Enfermedades producidas por el asbesto. México: Instituto Mexicano del Seguro Social, Subdirección General Médica; 1984.
4. Parkes W. Asbestos-related disorders. Br J Dis Chest 1973;67(4):261-300.
5. Parkes WR. Occupational lung disorders. Third edition. London: Butterworth; 1994.
6. Cano V, Núñez P, Cardoso R, Lugo P, Colinabarranco En: Barrios VG, Criales C. Pleura. México: Universidad Nacional Autónoma de México/Piensa; 1991.
7. Instituto Mexicano del Seguro Social. Memoria estadística de salud en el trabajo. México: IMSS; 2003.
8. Maldonado T, Méndez M. Enfermedades broncopulmonares de trabajo. En: Maldonado T, editor. Enfermedades por contaminación del ambiente de trabajo. México: Auroch; 1999.
9. Wagner JC. The sequels of exposure to asbestos dust. Ann N Y Acad Sci 1965;132(1):691-695.
10. Selikoff IJ, Hammond EC, Chung J. Carcinogenicity of amosite asbestos. Arch Environ Health 1972; 25(3):183-186.
11. Pan XL, Day HW, Wang W, Beckett LA, Schenler MB. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med 2005;172(8):1019-1025.
12. Morgan WK, Gee JBL. Asbestos-related diseases. En: Morgan WK, Seaton A, editors. Occupational lung diseases. Philadelphia: WB Saunders; 1995. p. 350-361.
13. Parkes WR. Asbestos-related disorders. Br J Dis Chest 1973;67(4):261-300.
14. Becklake MR. Asbestos-related diseases of the lung and other organs: their epidemiology and implications for clinical practice. Am Rev Resp Dis 1976;114(1):187-227.
15. Wyers H. That legislative measures have provedgenerally effective in the control of asbestosis. [Thesis Doctor of Medicine]. Scotland, UK: University of Glasgow; 1946.
16. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in North Eastern Cape Province. Br J Ind Med 1960; 17:260-271.
17. Wagner JC, Gilson JC, Berry G, Timbrell V. Epidemiology of asbestos cancers. Br Med Bull 1971; 27:71-76.
18. Newhouse ML, Berry G, Wagner JC. Turok ME. A study of the mortality of female asbestos workers. Br J Ind Med 1972;29(2):134-141.
19. Greenberg S, Hurst GA, Christianson SC, Matlage WJ. Pulmonary cytopathology of former asbestos workers. Report of the first year. Am J Clin Pathol 1976;66(5):815-822.
20. Méndez VM, Maldonado TM, Stanislawski EC, Mendoza HA. Mesotelioma maligno en un trabajador del asbesto. Rev Med IMSS 1982;20(3): 249-557.
21. Méndez V, Maldonado T. Tumores malignos relacionados con la exposición industrial al asbesto en México. Rev Med IMSS 1992;30(1):43-46.
22. Berry M. Mesothelioma incidence and community asbestos exposure. Environ Res 1997;75(1): 34-40.
23. Kjaergaars J, Michelsen E. Malignant mesothelioma incidence survival and relative risk in selected municipalities 1943-1992. Uerkrift Laeger 1997;159(31):4756-4761.
24. Boutin C, Schlesser M, Frenay C, Astoul P. Malignant pleural mesothelioma. Eur Resp J 1998;12 (4):972-981.
25. Yeung P, Rogers A. An occupational industry matrix analysis of mesothelioma cases in Australia 1980-1985. Appl Occup Environ Hyg 2001;16(1): 40-44.
26. Magnany C, Agudo A, González C, Andrion A, Calleja A, Chellini E, et al. Multicentric study on malignant pleural mesothelioma and nonoccupational exposure to asbestos. Br J Cancer 2000; 83(1)104-111.
27. Koskinen K, Pukkala E, Martikainen R, Reijula K, Karjalainen A. Different measures of asbestos exposure in estimating risk of lung cancer and mesothelioma among construction workers. J Occup Environ Med 2002;44(12):1190-1196.