Malignant mesothelioma risk factors: experience of the General Hospital of Mexico

Malignant mesothelioma (MM) is a rare neoplasm in Mexico, accounting for 2% of tumors of the thorax. However, from 1990 to 2000 a higher prevalence was observed, which sparked an interest in public health epidemiology. Some authors have mentioned this as a global epidemic.

Background: Malignant mesothelioma is a neoplasm with a poor prognosis. It is linked with asbestos contact; however, there are cases without this history. We undertook this study to investigate the relationship of asbestos exposure and other factors with malignant mesothelioma.

Methods: We carried out a retrospective analysis of histologically confirmed cases of malignant mesothelioma, familiar history of neoplasm, tobacco smoking, exposure to wood smoke and to asbestos. Logistic regression analysis was used with odds ratios.

Results: Sixty one cases of malignant mesothelioma were confirmed histopathologically: 41 males and 20 females. Mean age was 56 ± 13 years; 56 cases (91.8%) corresponded to epithelial malignant mesothelioma, three sarcomatous (4.9%), one desmoplastic and one biphasic. One in eight subjects (13.1%) had prior exposure to asbestos. Logistic regression model was used with four variables: family history of cancer, tobacco smoking, wood smoke and asbestos exposure, the last one with an OR = 3.083 and p >0.05. No other variables found to be a risk factor for malignant mesothelioma.

Conclusions: Asbestos exposure is a risk factor for malignant mesothelioma, which is confirmed in this study. However, it is important to extend the investigation of other possible causal factors of this disease.

Key words: malignant mesothelioma, asbestos, wood smoke exposure.

Introduction

MM originates in mesothelial cells with the pleura being the most frequent location; <10% of the cases are found in the peritoneum. MM shows a male predominance usually between 50 and 70 years of age. In the reported literature it was found that 80% of the cases are linked to exposure to asbestos dust. Other authors note figures of 80 to 33% without any history of contact with asbestos. Inhalation of wood smoke has been listed as a carcinogen that may be related to the MM even though no pathognomonic evidence exists.

The latency period between initial exposure and tumor appearance varies on average from three to five decades. Most new cases occur in subjects >60 years of age. Other mesotheliomas are related to previous radiotherapy and, in some there is a history of contaminated polio vaccines with the SV40 virus that exists in primates.

After diagnostic confirmation, the course of the disease is rapid and fatal. The most constant symptoms are progressive chronic dyspnea and diffuse chest pain. Additionally there may be pleural effusion, cough, asthenia, and adynamia that appears during the course of the disease.

Histologically, MM has different varieties: a) epithelioid comprising >50% of the cases, generally with a better prog-
nosis and life expectancy, b) corresponding to sarcomatoid in 7-20%, c) desmoplastic with 10-30%, d) mixed or biphasic occurring in 20-35% of the cases.

The objective of this study was to determine the frequency of MM and its relation to asbestos and other potential risk factors according to the experience in patients treated at the General Hospital of Mexico (HGM) from 1999 to 2009.

**Subjects and Methods**

A retrospective case-control study was conducted in the Service of Pneumology and Thoracic Surgery at HGM with patients diagnosed with histologically proven MM. Sixty one cases of MM were studied from January 1999 to December 2009. Variables analyzed were age, gender, and rural or urban residence. Some possible risk factors for malignant mesothelioma were similarly analyzed such as smoking, wood smoke inhalation, history of occupational or environmental contact with asbestos, family and personal history of neoplasm.

Histopathological study was reviewed by a certified pathologist who was an expert in tumors. Immunohistochemistry method was used with the following markers: calretinin, cytokeratin, Wilm’s tumor -1 (WT-1), E-cadherin, TTF-1, and HBME. Reported symptoms were noted in the clinical files: dyspnea, chest pain, cough, weight loss, fatigue, weakness and pleural effusion.

The 61 cases of MM were matched with 130 patients with non-neoplastic diseases as controls for age and gender with a ratio of 1:1-3. MM analysis and potential risk factors were analyzed with a multiple logistic regression model using the statistical computer program STATA v.10. Independent variables were history of cancer, smoking, exposure to wood and asbestos exposure. Each of the variables was analyzed dichotomously and noted as the presence or absence of exposure.

**Results**

MM was represented in 10% (61 cases) of all treated chest malignancies (601 cases) in the period from 1999 to 2009 at HGM. Of the 191 cases that comprised this analysis, 61 had MM and 130 had non-neoplastic pathologies, the latter being selected as age- and gender-matched controls. The average age of patients with MM was 56 ± 13 years, with the highest frequency in males aged 61 to 70 years, followed by those in the 51- to 60-year-old group.

Of the MM cases, 41 (67.2 %) were males and 20 (33%) were females; 80% lived in urban areas and 20% in rural areas. Tobacco consumption was recorded in 20 (32.8%) patients, with an average index of 15 packs per year. Eight females had a history of family tumors (three with breast cancer, four with cervical cancer, and one with gastric cancer). In 12 cases there was exposure to wood smoke.

Of the patients diagnosed with MM, 100% experienced symptoms of chest pain, cough, dyspnea, weight loss, fatigue and adynamia. Only eight cases (13.1 %) (seven males and one female) had a history of occupational exposure to asbestos, all with histopathological diagnosis of epithelial MM. Radiographic images suggestive of MM according to chest x-ray and computed tomography (CT) were unilateral in 48 patients (78%) and bilateral in 13 (21%). There were 49 cases (80%) (Figure 1) with pleural effusion. Altered mediastinal pleural image was found in three patients and consisted of festooned thickening of the parietal pleura with a lesser amount of mediastinal pleural thickening (Figures 2 and 3). MM predominated in stage III with 33 cases (54%), 23 males and 10 females, followed by stage IV in 19 patients (31%), 14 males and 5 females. Seven cases of stage II were observed (11%) and stage I included two cases (3%).

Histological diagnosis was performed on transthoracic pleural biopsies with Abrams needle in 34 of the cases (56%) and through direct thoracoscopic biopsy or video-assisted minimal thoracotomy in 27 (44%) patients. The histologic origin in 56 of the cases (91.8%) was epithelioid (37 males and 19 females), sarcomatoid in three cases (4.9%), desmoplastic in one and biphasic in another. These last cases were males (Figure 4).

Logistic regression models were analyzed where the dependent variable was MM and the independent variables were family history of cancer, smoking, and exposure to wood smoke and asbestos. Various interactions of the independent variables were performed but none resulted to be statistically significant. In the final model, only four initial variables were included. Of these, asbestos exposure had an odds ratio of 3.083 with a statistical significance ($p <0.05$), confirming the association between asbestos and MM that was reported in the literature. The remaining variables included in the model were not found to be a risk factor for MM (Table 1).

**Discussion**

According to the documented experience at HGM in the Service of Pneumology and Thoracic Surgery, of the 191 cases that constituted this analysis, it was determined that MM was more frequent in males (67.2%), especially in the fifth and sixth decades of life, which probably involves a long latency period considering that most were urban dwellers.
The association with asbestos was similar to the distribution found by other authors in Mexico; nevertheless, in the data analyzed in this study, this association resulted in being nonsignificant, independent of the well-established fact of the association of MM and asbestos. Symptoms of chest pain, cough, dyspnea, asthenia and adynamia occurred in all patients diagnosed with MM. The presence of pain and weight loss is characteristic of an advanced disease and represents a poor prognosis in cases analyzed with MM; 52 patients were in advanced stages (stages II and III of the disease). In cases of diagnostic uncertainty, examination by electron microscopy allowed for the differentiation with adenocarcinoma.

The consulted literature indicates that exposure to asbestos is the major risk factor found in 80-90% of cases of MM; however, in the data analyzed in this study it was observed that 86.9% of the cases had no history of contact with asbestos. In addition, this variable was found to be nonsignificant in the logistic regression model. Therefore, it is advisable to conduct future studies to seek other risk factors as the cause of MM.

Etiologically, asbestos exposure has been reported as the most important risk factor (80%). Because only 5-17% of exposed individuals develop MM, the direct relationship between the two is uncertain, proposing a pathophysiogenic multifactorial framework, particularly in cases with no history of contact with asbestos. In addition, this variable was found to be nonsignificant in the logistic regression model. Therefore, it is advisable to conduct future studies to seek other risk factors as the cause of MM.

In the multifactorial process, genetic factors on chromosomes 1p, 6q, 9p, 13q, and 14q(2-12-13) have also been involved; the loss of one copy of chromosome 22, monosomy 4 and 7, p16, p14ARF, NF2, and p53 mutations that have been identified in MM. Its association with asbestos has been confirmed. In addition there is a suggestion of an autosomal dominant inheritance pattern. The possibility that MM has a hereditary factor seems attractive; how-
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The simulated SV40 virus in poliovirus vaccines seems to favor MM. Although there is no definitive evidence that tobacco increases the risk of the disease, a relationship has been found between the existence of prior radiation and post-tuberculosis calcification with cases of MM. 

Exposure to other mineral fibers such as erionite, potassium hydrate, sodium, calcium, magnesium, aluminum silicate in Turkey and tremolite (calcium silicate and silicate hydroxide magnesium) in Greece is related to MM. Other fibers are crocrolide and ammonite with latency periods of exposure for the development of MM varying from 44.9 to 51 years, respectively.

Other possible causes are synthetic fibers as risk factors for the development of MM. Carbon nanotubes have been shown to produce inflammatory changes and induce mesothelioma in experimental models.

These considerations suggest that individual susceptibility and the involvement of other carcinogens not identified in the Mexican population may play a decisive role for the development of MM.

In conclusion, pleural MM showed a casuistry of 10 years increased caution for this neoplasm, constituting 10% of all chest malignancies. None of the cases were asymptomatic and suspected pleural effusion was the presenting complaint. Most were diagnosed in stages III and IV with invasion of the chest wall and mediastinal structures without the possibility of radical surgical treatment and with a poor prognosis. According to the retrospective case-control study conducted in the HGM in the Service of Pneumology and Thoracic Surgery and considering that in 86.9% of the analyzed data there was no history of exposure to asbestos. It is important to consider other etiological factors in the population studied. In the case of MM, we must consider other risk factors even in patients without documented exposure to asbestos, which represents an opportunity for diagnosis so that MM is not considered only as a diagnosis of exclusion. It is also important to include the analysis of possible genetic factors that may be associated with this disease.

Table 1. Logistic regression model (risk factors for malignant mesothelioma)

| Risk Factor         | OR    | SE   | z     | p >|z|   | 95% CI  |
|---------------------|-------|------|-------|------|-----|--------|
| History of cancer   | 0.906 | 0.534| -0.17 | 0.868| 0.285, 2.880 |
| Smoker              | 0.123 | 0.044| -5.86 | 0.000| 0.061, 0.248  |
| Wood exposure       | 1.041 | 0.454| 0.09  | 0.925| 0.442, 2.450  |
| Asbestos exposure   | 3.083 | 1.891| 1.84  | 0.066| 0.929, 10.259 |

n = 191. LR $\chi^2 (4) = 42.06$, Prob $>\chi^2 = 0.0000$, Logarithm of verosimilitude, -98.610813, Pseudo R2 = 0.1758.

OR, odds ratio; CI, confidence interval; SE, standard error.

References