Malignant Pleural Mesothelioma Due to Environmental Mineral Fiber Exposure in Turkey* Analysis of 135 Cases Ziya Toros Selçuk, M.D.; Lütfi Çöplü, M.D.; Salih Emri, M.D.; Ali Fuat Kahveci, M.D.; Ahmet Altay Şahin, M.D.; and Yusuf İzzettin Barış, M.D., F.C.C.P.

We reviewed data from 135 patients with environment-associated malignant pleural mesothelioma (MPM) from the Central Anatolian region of Turkey. The most significant factors suggesting the diagnosis of MPM were the village where the patient resided and the typical presenting symptoms and signs of unilateral exudative pleural effusion associated with nonpleuritic chest pain. Computed tomography and ultrasonography were very useful for evaluating the extension of the tumor in the thoracic and abdominal cavities and chest wall. The tissue diagnosis was established by either thoracoscopy (39 percent) or pleural biopsy (39 percent) in the majority of the cases. The median survival after diagnosis was 13.52 months for erionite-associated MPM and 21.56 months for asbestos-associated MPM. The actuarial survival curves for the fibrous minerals were significantly different for survival computed both from onset of the symptoms and after diagnosis. Medical or surgical treatment or both did not change the outcome of the disease.

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Malignant pleural mesothelioma (MPM) frequently is caused by environmental and occupational exposure to asbestos. Crocidolite and amosite are the main asbestos types causing occupation-associated MPM. However, tremolite is the type of asbestos most often associated with environmental MPM as reported in Turkey, Greece, and Cyprus.1-5 Asbestos was the first but not the only mineral fiber implicated as a cause of mesothelioma. Erionite, a natural fibrous zeolite, which can be found in volcanic tuffs, is an environmental contaminant in the Cappadocia region of Central Anatolia. The high potential of erionite to induce MPM has been confirmed by both epidemiologic6-10 and experimental studies.11-15

Three villages, namely Karain, Tuzköy, and Sarihidir, in the Cappadocia region of Central Anatolia are considered “erionite” villages. These villages are built upon and into volcanic rocks containing erionite. Although fiber levels were low, high proportions of erionite were detected in airborne dust samples collected from the environment.8,10

Retrospective mortality studies of the erionite villages between 1980 and 1988 are published elsewhere.16 Although many villagers had already migrated, recent mortality studies have included all those who had died either in the villages or outside. From 1988 to 1990 there had been additional deaths due to MPM in these erionite villages. Taken together, there were a total of 347 deaths between 1980 and 1990 in Tuzköy, and 80 (23.1 percent) of these were due to MPM. In Karain, between the years 1970 and 1990, there were a total of 249 deaths, 126 (50.6 percent) being due to MPM. Epidemiologic and case-control studies in three erionite villages have shown the incidence of malignant mesothelioma to be 1,000 times higher than the reported general population incidence elsewhere in the world.17,18 Nonmalignant changes such as diffuse pleural thickening, localized pleural fibrosis, pleural calcification, benign pleural effusion, and diffuse lung fibrosis also were found to have a high prevalence in these erionite villages. In vivo and in vitro experimental studies have shown that erionite is the most powerful fibrous carcinogen so far studied.

There are many asbestos deposits in some rural parts of central and eastern Anatolia. The type of asbestos found in most of this region is either tremolite or chrysotile asbestos, which has no economic value.1 However, villagers use asbestos-contaminated soil (white soil) as a whitewash or plaster material (white stucco), as a substitute for baby powder, on roofs for insulation and prevention of water leakage, etc. One of the most important routes of domestic exposure is from dust originating from the walls of homes that have been whitewashed with white stucco. In the recent past, Turkish and Greek villagers used asbestos-contaminated soil as “white stucco” because of its brilliant whiteness and also because it does not stain easily. (Asbestos is derived from the Greek word

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CFF = chronic fibrosing pleuritis; CFP = calcified pleural plaques; MPM = malignant pleural mesothelioma; US = ultrasonographic

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*amiantos*, meaning spot-free.) The major occupations of the population in rural parts of central and eastern Anatolia are agriculture and livestock breeding. These populations do not differ with respect to demographic and socioeconomic variables. There is no exposure to asbestos, either through an occupational origin or from the use of any asbestos product. Yet MPM cases originated from those villages with only environmental asbestos exposure where all patients had admitted the domestic use of asbestos-contaminated soil.

Malignant pleural mesothelioma is one of the major health problems facing Turkey today. This is mainly due to environmental exposure to asbestos and erionite. In this study, we report our findings on 135 patients with MPM due to environmental exposure to either asbestos or erionite who were seen at Hacettepe University Hospital between the years 1980 and 1990.

**Patients and Methods**

A thorough review of the patient records of Hacettepe University Hospital disclosed 183 patients with MPM who were seen between January 1981 and December 1990. Of these, 48 patients were excluded because of incomplete clinical and radiologic data. The diagnosis of MPM was confirmed by the pathology department of Hacettepe University Hospital. The patients were divided into two major groups depending on the type of environmental mineral fiber exposure, asbestos or erionite. All members of the erionite group were from the aforementioned three villages, namely Tuzköy, Karain, and Sarpıdhır, whereas those of the asbestos group were from more than 30 villages also in the Central Anatolian region. In all these villages there is no commercial use of asbestos or erionite, no asbestos or erionite industry, and no history of occupational exposure to either asbestos or erionite. Clinical information, including age, sex, smoking status, birthplace, history of occupational and environmental exposure to mineral fibers or chemicals, previous irradiation, duration and character of symptoms, and clinical findings at presentation, were extracted from the patient records. General malaise, weight loss, and loss of appetite were grouped as constitutional symptoms. Lack of ipsilateral hemithoracic respiratory maneuvers along with prominent volume loss were regarded as frozen chest.

Since the pathologic subtyping of mesothelioma was recorded in less than half of the patients in the pathology records at the time of diagnosis, this information is eliminated. Staging was performed according to the system proposed by Butchard et al. either at presentation or retrospectively. Thoracotomy was performed on 20 patients and autopsy on only one. Because of inadequate clinical and radiologic information, 12 patients, all from the erionite group, were excluded from staging.

Pleural biopsies were obtained with an Abrams needle and thorascopic examination was performed with the patient under local anesthesia. Chest x-ray films at presentation were available in all patients and were reviewed by a panel of five chest physicians. Computed tomography (CT) of the chest, where available, was reevaluated by the same group, who were unaware of either the chest x-ray film or clinical findings. Ultrasonographic (US) findings at the time of presentation also were extracted from the patient records.

Survival data, when available from patient records or provided by the local authorities, were noted. The treatment regimes varied greatly and a combination of modalities frequently was employed. The treatment regimens were not reported separately in view of the small numbers of patients in each group and the indifferent impact of treatment on survival.

The Student *t* test, chi-square test, Fisher exact test, and analysis of variance were used for analysis of the data. Probability values less than 0.05 were considered statistically significant. Due to the small number of cases of stage IV disease, these patients were combined with the patients who had stage III disease. Analysis of survival of these patients according to grouping factors was performed with the BMDP statistical software package using the Mantel-Cox method. The closing date for the study was January 1, 1991. Analysis of survival is both from the onset of symptoms and after establishment of the diagnosis.

**Results**

There were 58 MPM patients from the erionite villages and 77 patients from the asbestos villages. The mean ages were 46.4 ± 10.6 years for the erionite-exposed group, 49.7 ± 11.7 years for the asbestos-exposed group, and 48.3 ± 11.0 years for the overall group. Age of the patients ranged from 27 to 67 years in the erionite-exposed group and 26 to 75 years in

**Figure 1.** Distribution of 135 mesothelioma patients according to age and mineral exposure. The predominance of persons younger than 41 years of age in the erionite-exposed group was found to be significant (chi-square test, 4.05; *p* = 0.044).
the asbestos-exposed group. The male-female ratios were 31:27 for the erionite-exposed and 51:26 for the asbestos-exposed patients. Distribution of the 135 patients according to age and exposure to the type of mineral fibers is shown in Figure 1. The mean and median durations between the beginning of the symptoms and presentation were 5.6 and 4 months, respectively, with a range of 1 to 38 months.

The most prominent symptoms at presentation were dyspnea (80 percent), nonpleuritic chest pain (71 percent), constitutional symptoms (64 percent), and cough (55 percent). Shoulder pain, fever, and abdominal discomfort were rare symptoms. Signs compatible with pleural effusion were detected in the majority of cases (91 percent). Symptoms and signs are not statistically different between the asbestos- and erionite-exposed groups. However, lymphadenopathy was more frequent in the erionite-exposed group (10 vs 3); clubbing, in the asbestos-exposed groups (6 vs 0) (chi square test, p<0.01; Fisher exact test, two-tailed, p<0.05, respectively). At presentation the tumoral process was confined to only one hemithorax, the right in 77 cases (57 percent) and the left in 57 (42 percent). The exception was one patient who was diagnosed at autopsy and who had extensive disease involving both sides. The right hemithorax was more frequently affected in both groups, 55 percent in the erionite-exposed group and 60 percent in the asbestos-exposed groups. Though volume loss of the affected hemithorax was frequently observed at presentation or during follow-up, four cases (3 percent) presented with unilateral hypertrophy of the chest. This was due to the presence of massive pleural effusions in three cases and also was observed in one without an effusion because of tumoral involvement of the chest wall.

Frozen chest was detected in 21 (16 percent) cases at presentation. Abdominal mass was present in 13 (10 percent) and extrathoracic mass in three (2 percent) patients. Implantation of the tumor in the tract of either the thoracotomy incision or the pleural biopsy sites occurred in 13 (10 percent) cases. All the patients in the late stage of the disease suffered severe, intractable pain but some of the patients with tumor implantation in thoracotomy scars developed this severe, intractable chest pain earlier. Superior vena cava and Horner syndromes at presentation were detected in three and two patients, respectively. During follow-up, depression of the shoulder and frozen chest was noted in 14 (10 percent) patients, two patients developed superior vena cava obstruction and one patient developed Horner's syndrome. At presentation, one of the patients was admitted for investigation of fever. In two patients, tumor caused fatal pericardial tamponade in the later stages of the disease. Scalp metastasis was detected in one patient in the terminal stages of the disease. Also a brain metastasis developed in one patient. Thrombosis in the inferior vena cava and portal vein along with abdominal extension of the right-sided tumoral lesion occurred in the terminal stage of the disease in one patient with asbestos-associated mesothelioma.

Methods of diagnosis of 135 patients are reviewed in Table 1. Because of nondiagnostic or indeterminate results of samples taken by closed pleural biopsies, the diagnosis was established by thoracoscopy in five patients and by thoracotomy in two patients. By thoracoscopy, intrathoracic structures other than the pleura could not be evaluated due to numerous fibrous bands and thick adhesions in the pleural cavity of six patients. These six patients are excluded from those whose thoracoscopic findings are presented in Table 2. The volume of the pleural effusions ranged from 200 to 6,000 ml, with a mean of 2,700 ml. High viscosity of the pleural fluid was found in only eight (17 percent) patients; hyaluronic acid levels were not measured. The diameter of the nodules observed on the parietal or visceral pleura, or both, ranged from a few millimeters to 3 cm, the majority being less than 10 mm. The nodules were concentrated on the diaphragmatic pleura and on the lower part of the visceral and parietal pleura. There was no apparent morbidity

| Table 1—Methods of Diagnosis of 135 Mesothelioma Patients |
|---------------------------------|-----------------|-----------------|-----------------|
| **Diagnostic Method** | **Erionite-Exposed Group (%)** | **Asbestos-Exposed Group (%)** | **Total (%)** |
| Pleural biopsy | 25 (48) | 25 (32) | 53 (39) |
| Thoracoscopy | 17 (29) | 35 (45) | 52 (39) |
| Thoracotomy | 7 (12) | 13 (17) | 20 (15) |
| US-guided biopsy | 5 (9) | 2 (3) | 7 (5) |
| CT-guided biopsy | 1 (2) | 1 (1) | 2 (1) |
| Autopsy | 1 (0) | 1 (1) | 1 (1) |
| Total | 58 | 77 | |

**Table 2—Thoracoscopy Findings in 46 Mesothelioma Patients**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Erionite (%)</th>
<th>Asbestos (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 9)</td>
<td>(n = 37)</td>
<td>(n = 46)</td>
<td></td>
</tr>
<tr>
<td>Crowding</td>
<td>4 (44)</td>
<td>19 (51)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>High viscosity</td>
<td>3 (33)</td>
<td>5 (14)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Encasement</td>
<td>6 (66)</td>
<td>21 (57)</td>
<td>27 (59)</td>
</tr>
<tr>
<td>CFP</td>
<td>3 (33)</td>
<td>9 (22)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>CPP</td>
<td>3 (33)</td>
<td>5 (14)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Pleural thickening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>9 (100)</td>
<td>37 (100)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>Visceral</td>
<td>7 (77)</td>
<td>20 (54)</td>
<td>27 (59)</td>
</tr>
<tr>
<td>Nodular lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal pleura</td>
<td>7 (77)</td>
<td>35 (95)</td>
<td>42 (91)</td>
</tr>
<tr>
<td>Visceral pleura</td>
<td>6 (66)</td>
<td>26 (70)</td>
<td>32 (70)</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>8 (88)</td>
<td>33 (89)</td>
<td>41 (89)</td>
</tr>
<tr>
<td>Mediastinal pleura</td>
<td>4 (44)</td>
<td>20 (54)</td>
<td>24 (52)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>6 (66)</td>
<td>25 (68)</td>
<td>31 (67)</td>
</tr>
</tbody>
</table>

*Thoracoscopic findings were not statistically significant between the erionite- and asbestos-exposed groups.
There or pushed or astinal and the thickened were through been pneumothorax effusion. was in significant US mortality percent cases of asbestos hemithorax from lung of the ipsilateral side was recognized in 16 (28 percent) erionite-exposed and 40 (52 percent) asbestos-exposed patients. The ratio of observed CPP between the groups was not significantly different, whereas the ratio of CFP was (chi square test, p>0.05 and p<0.01, respectively).

After exclusion of 12 (9 percent) patients with erionite-associated MPM from the study group due to inadequate data, 123 patients were staged according to a modified system proposed by Butchard et al. A total of 64 cases (52 percent), 23 from the erionite-exposed and 41 from the asbestos-exposed groups had stage 1 disease at presentation; 11 and 12 erionite-exposed patients and 15 and 18 asbestos-exposed cases had stage 2 and 3 disease, respectively. Only three patients from the asbestos-exposed group had stage 4 disease at presentation.

Of the 135 patients, 30 (22 percent), 24 asbestos-exposed and six erionite-exposed patients, were alive at the end of the study; 39 (29 percent) patients, all from the asbestos-exposed group, were unavailable for follow-up. The 66 (49 percent) patients who were followed up until death consisted of 52 erionite-exposed and 14 asbestos-exposed patients. There was only one person from the erionite-exposed group who survived more than five years. The cases that were unavailable for follow-up were compared for a number of variables with those of the asbestos-exposed group who were followed up until death or to the end of the study period.

The difference between these two groups was significant for sex, treatment status, and age of the disease at presentation, but not for age, duration of symptoms, or side of the hemithorax involved (sex: chi square test, p<0.05; treatment status: chi square test, p<0.01; stage: chi square test, p<0.05; age: t test, p>0.05; duration of symptoms: t test, p>0.05; side of lesion: chi square test, p>0.05).

After exclusion of the cases unavailable for follow-up, sex, treatment status, and stage were investigated for their impact on survival of the asbestos-exposed cases. Only sex was found to be significant (Mantel-Cox, p<0.05). The median survival after diagnosis was 13.52±0.73 months for the erionite-exposed group and 21.56±0.77 months for the asbestos-exposed group. The difference in median survival between the asbestos- and erionite-exposed patients was significant (Mantel-Cox, p<0.01[Fig2]). The observed differences were at the second, fifth, sixth, seventh, eighth, and 12th three-month periods.
68 ERIONITE, 77 ASBESTOS PATIENTS

This significance was also apparent for survival estimated from the onset of symptoms (Mantel-Cox, p<0.01). Median survivals from the onset of symptoms for the erionite- and asbestos-exposed patients were 16.80 ± 0.66 and 36.16 ± 1.50 months, respectively. Survival ratios of MPM cases after diagnosis at 12 and 24 months were 64 and 15 percent for the erionite-exposed and 79 and 42 percent for the asbestos-exposed groups. Survival ratios at 12 and 24 months from the onset of symptoms were 78 and 30 percent for the erionite-exposed and 92 and 69 percent for asbestos-exposed groups. The differences of actuarial survival curves between asbestos- and erionite-exposed patients, both from the onset of symptoms and after diagnosis, persisted with analysis stratified for sex (Mantel-Cox, adjusted for strata, p<0.01).

Presence of dyspnea, chest pain, constitutional symptoms, age less than 50 years, less than three months' duration of symptoms, presence of pleural effusion, stage of the disease at presentation, and treatment status had no impact on survival, either from the onset of symptoms or after the diagnosis was established, for the erionite-exposed patients. Comparison of actuarial survival curves with sex taken as a prognostic factor and stratified for treatment gave negative results for the erionite-exposed group (Mantel-Cox, p>0.05). Treatment taken as a prognostic factor and stratified for sex gave negative similar results in the erionite-exposed group (Mantel-Cox, p>0.05).

**DISCUSSION**

Environmental asbestos or erionite exposure was documented in all of the cases in this study. Fifty-eight MPM cases (40 percent) originated from the three erionite villages, whereas only 77 MPM cases were derived from the more than 30 asbestos villages. The 135 cases reported have considerably lower mean and median ages compared with those in the literature. One quarter of MPM patients were less than 40 years of age. This difference may be due to early onset of nonoccupational exposure to either mineral. The mean ages of the asbestos- and erionite-exposed groups were not significantly different. The exposure to either mineral begins at birth, and in the erionite villages, mesothelioma has been diagnosed even in patients who had left the villages after the age of 12 years. These results suggest that the rather long latent period required for the development of MPM is irrespective of the type of mineral fiber one is exposed to and confirm past experimental and epidemiologic findings regarding the high carcinogenic potential of erionite.

Males and females are approximately equal in number in the erionite-associated MPM group. The male predominance is apparent only in the asbestos-associated group. Although the sex difference in the latter instance is compatible with the literature, it may be explained in part by referral bias. Populations from the three erionite villages already are known as a high-risk group for malignant disease, and the patients are referred as soon as a presumptive diagnosis is made. In contrast, there is no equivalent system of survey in the asbestos villages. Asbestos deposits are quite widespread in Central Anatolia; thus, there is no focal origin for asbestos-associated MPM. Patients are not "actively" surveyed but are admitted after presentation. The male dominance in the asbestos group might also have evolved through the more frequent use of hospital services by the male population when compared with females in rural parts of Turkey.

The duration of symptoms prior to presentation was not significantly different between the erionite- and asbestos-exposed groups. Duration of the symptomatic
period is similar to that reported in the literature.\textsuperscript{21,23} The tumor was in the right hemithorax in the majority of cases. Nonpleuritic chest pain and dyspnea were the most common symptoms. A common finding was constriction of the ipsilateral lung by the tumor mass, causing volume loss. Along with the classic symptoms and findings of MPM, uncommon presentations such as ipsilateral chest hypertrophy, superior vena cava obstruction, and Horner's syndrome also were encountered in a minority of the patients. Though clinical findings consistent with pleural effusion were present in 91 percent of the cases, its presence was confirmed in only 72 percent. This may be due to the presence of diffuse pleural thickening and restriction of respiratory maneuvers. The most significant factors suggesting the diagnosis of MPM were the village where the patient resided and the typical presenting signs and symptoms of unilateral exudative pleural effusion associated with nonpleuritic chest pain.\textsuperscript{24} Approximately half of the patients in both groups had presented with stage 1 disease, and a quarter of each of them were in stage 2 and 3, with only a minority in stage 4.

Chest x-ray films were notable for the presence of pleural thickening and/or lobulated pleural masses. As the fibrous component of the tumor encases the lung, volume loss, depression of the ipsilateral shoulder, and frozen chest occur. Involvement of the mediastinal pleura and the interlobar fissure are better delineated by CT than by chest x-ray films alone.\textsuperscript{25} The presence of CPP also can be a reminder to include MPM in the differential diagnosis of a patient with unilateral effusion.

Local infiltration of tumor into the chest wall, mediastinal structures, and the abdominal cavity through the diaphragm was common in the late stage of MPM.\textsuperscript{26} Also, distant visceral metastasis may occur. As a noninvasive imaging technique, US was found to be very useful at showing the invasion pattern, as well as metastasis in abdominal organs such as liver, kidney, adrenal gland, and peritoneum. Thrombosis of the inferior vena cava and portal vein was an uncommon complication during the course of MPM and had not been previously reported. There was also one case of scalp metastasis.

Our study also shows that pleural biopsy and thoracoscopy are the most useful diagnostic tools for the tissue diagnosis of MPM, providing the diagnosis in more than three quarters of the patients. Thoracoscopy is a method for both diagnosis and staging of the MPM.\textsuperscript{27} Multiple, small neoplastic nodules on the parietal pleura are typical of MPM, in contrast to nodules located in the visceral pleura as seen in metastatic pleural carcinoma. We did not observe false-positive results or life-threatening complications with thoracoscopy. However, thick adhesions and fi-


