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Features of Asbestos-Exposed and Unexposed Mesothelioma

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Thirty-six histologically confirmed cases of pleural and peritoneal mesothelioma have been observed in a chest unit over a period of 53 months. The past asbestos exposure was assessed by a standardized questionnaire in all cases and the asbestos lung burden was determined by means of mineralogical analysis of lung-related biological specimens (sputum, bronchoalveolar lavage fluid, lung tissues) in 28 cases. The results of these two methods were found in good agreement. Past asbestos exposure has been definitely implicated in 17 cases and definitely eliminated in 10 cases. The results were nonconclusive in other cases. The group with definite past asbestos exposure was different from the nonasbestos-exposed group by clinical, biological, pathological, and prognosis features that were analyzed. In cases without past asbestos exposure there were no other possible causative agents. Younger age and similar incidence in men and women suggest an environmental or natural disease.

Key words: mesothelioma, asbestos, fiberglass, paraffin, radiodiagnostic irradiation, non-asbestos exposure

INTRODUCTION

Mesothelioma is a rare tumor, but significantly associated with past occupational exposure to asbestos [Greenberg and Lloyd Davies, 1974; Selikoff, 1976]. More recently, an association between mesothelioma and exposure to erionite-zeolite fibers has also been highly suspected in Turkey [Artvinli and Baris, 1979]. The mesothelioma registries conducted in various countries reveal widely differing proportions of cases with past asbestos exposure (from 20% to 72%). However, in all these studies there was a significant proportion of histologically confirmed mesothelioma in which past occupational asbestos exposure has been definitely eliminated; the consecutive mesotheli-

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oma cases referred to a chest hospital unit in the district of Val de Marne, France (1.2 million inhabitants) have been investigated in order (1) to study the percentage of asbestos-related mesothelioma by means of standardized questionnaires; (2) to compare the number of coated fibers in sputum and/or lung tissue samples in asbestos-related and nonasbestos-related mesothelioma; (3) to discover in the mesothelioma cases not related to asbestos a possible significant association with other occupational hazards; and (4) to compare on the basis of clinical, radiological, histological, and etiological data the asbestos-related and nonasbestos-related mesothelioma.

MATERIALS AND METHODS

Thirty-six mesotheliomas (34 pleural and 2 peritoneal) have been observed between October, 1976 and February, 1981. In all cases, the diagnosis was based on pathological specimens. Mantoux test with 0.1 ml of purified protein derivative RT 23 was performed [Deck and Guld, 1964]. Chest X-rays (posteroanterior, lateral, and 45° oblique films) [Mackenzie and Harries, 1970] were classified by two readers (LDM and AH) according to the International Classification of Pneumoconiosis 1980 [Hirsch, 1979]. A cytological and biochemical analysis of pleural fluid was carried out including the measurement of hyaluronic acid content [Boersma et al, 1980]. Pathological specimens of the pleura were obtained either by one or iterative-needle biopsies and, since June, 1979, by thoracoscopy under general or local anesthetic [Bourin and Viallat, 1980]. This technique provided a good view of the parietal and visceral pleura and made it possible to obtain large samples of tissue. An open thoracotomy or laparotomy was needed in a few cases. All tissue samples were reviewed for pathological confirmation using light microscopy, and electron microscopy when necessary [Stoebner et al, 1979], by the pathologists of the French Mesothelioma Register.

The following data were collected by means of a standardized questionnaire designed to investigate causative agents: previous chest diseases and radiodiagnosis irradiation of the thorax; smoking habits (expressed in pack/year); occupational, para-occupational, environmental, and domestic past exposure to asbestos according to the criteria proposed by the European Communities [Zielhuis, 1977]; complete work histories using a standardized questionnaire designed to detect other occupational hazards and administered directly to the patients by LDM.¹ In 28 cases, measurement of asbestos fibers was carried out in various biological specimens: coated fibers in sputum and/or bronchoalveolar lavage fluid samples (light microscopy) and in lung tissue (digestion-microfiltration method) [Bignon et al, 1974; Gaudichet et al, 1979; Sébastien, 1980, 1982].

Results have been analyzed using Student's t-test and chi-square approximation. Probabilities (p values) equal to or less than 0.05 were considered significant.

RESULTS

Pathological and Clinical Data

During the 53-month duration of this study, pathological samples from 45 cases were submitted to the National Mesothelioma Register Panel: 36 cases have been con-

¹Questionnaire samples are available from the editorial staff of the Journal.

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firmed histologically as mesothelioma. The histological type was epithelial in 30 cases, fusiform in 2 cases, and mixed in 4 cases. The other nine cases were excluded: 3 had insufficient material, 5 cases were classified secondary pleural adenocarcinomas, and 1 case was pleural sarcoma. The pathological diagnosis was possible by analyzing pleural specimens obtained in 6 cases by one-needle biopsy, in 3 cases by two- or three-needle biopsies, in 9 cases by thoracoscopic biopsies, in 14 cases by open chest biopsies, in 1 case by mediastinoscopic biopsy, and in 1 case by laparoscopic biopsy. In two cases, the diagnosis was made at autopsy.

In the 36 confirmed cases, the chief complaints were dyspnea on exercise (47%) and chest pain (37%). In two cases (cases 12 and 19), a routine screening chest X-ray showed pleural opacities. The first pleural fluid collected was exudative in 96% of cases; it was clear in 67%, bloody in 30%, and opaque in 3% of cases. No particular cytological pattern was noted from the examination of pleural fluid.

Etiological Data

On the basis of the standardized asbestos questionnaire, the 36 mesotheliomas were divided into four groups: (1) 7 cases with heavy, definite, past asbestos exposure; (2) 10 cases with moderate, definite, past asbestos exposure; (3) 10 cases without definite, past asbestos exposure; and (4) 9 cases with inconclusive questionnaires. In the seven heavy, definite, past asbestos-exposure mesotheliomas (Table I), all patients were male; the tumor was epithelial in 57%, all the mineralogical analyses performed were positive, and asbestos pleural or parenchymal contralateral radiological abnormalities were present in 71%. In the 10 moderate, definite, past asbestos-exposure mesotheliomas (Table II), 2 patients were female, one with household contact (case 8); the length of asbestos exposure (30.3 ± 8.2 years) was significantly greater ($p < 0.001$) than in the heavy, definite, past asbestos-exposed group (11.4 ± 9.5 years), the tumor was epithelial in 80%, the mineralogical analyses were positive in all cases, and asbestos pleural or parenchymal contralateral radiological abnormalities were present in 80%. In the 10 nonasbestos-related mesotheliomas (Table III), 4 patients were female and all the tumors were of epithelial type. In 3 out of the 6 investigated cases, mineralogical analyses were positive for asbestos bodies but at a very low level, except in case no. 27, where 6,903 coated fibers per gram of dried lung tissue have been found. Asbestos-related radiological abnormalities were seen in one case. In the 9 inconclusive cases (Table IV), 5 patients were female and 89% of the tumors were of epithelial type. In 6 out of the 7 investigated cases, the mineralogical analyses were positive, and asbestos pleural or parenchymal radiological abnormalities were seen in 44% of the cases.

Comparison Between Clinical, Histological, Radiological, and Biological Parameters in the Heavy and Moderate Definite Asbestos-Related Mesotheliomas and in the Nonasbestos-Related Mesotheliomas

Several parameters were different between asbestos-related and nonasbestos-related mesothelioma (Table V). In the nonasbestos-related group, (1) patients were younger; (2) their mean survival time was longer; (3) the diameter of PPD test was greater; (4) the contralateral chest X-rays opposite to the mesothelioma showed no asbestos-related abnormalities; (5) the sex ratio male to female was 1.5 for unexposed cases and 7 for exposed cases; and (6) the tumors of exposed cases were of various histological types while unexposed cases were only of epithelial types. The nonasbestos-related mesotheliomas were diagnosed by open thoracotomy in 50% versus 35% in the asbestos-related mesotheliomas.

TABLE 1. Clinical and Mineralogical Features in Seven Heavy, Definite, Past Asbestos-Exposure Cases

Occupation	No.	Sex	Age	Histological type	Asbestos exposure (questionnaire)		No. coated fibers in			Contralateral radiological abnormalities
					Duration (years)	Latency period (years)	Sputum	BALF (ml)	Dried lung (gm)	
Asbestos-cement hen house builder	1	M	56	E	13	15				—
Battery-box manufacturer	2	M	66	M	5	32	16	1,441		+
Steam-fitter	3	M	72	F	1	36			1,183	—
Locomotive insulator	4	M	69	E	12	55	3			+
Boilermaker	5	M	55	E	16	35				+
Asbestos-joint cutter	6	M	62	E	2	26	3		1,430	+
Asbestos-sprayer	7	M	59	M	31	31				+

Key words: E = epithelial, M = mixed, F = fusiform, BALF = bronchoalveolar lavage fluid.

TABLE II. Clinical and Mineralogical Features in Ten Moderate, Definite, Past Asbestos-Exposure Cases

Occupation	No.	Sex	Age	Histological type	Asbestos exposure (questionnaire)		No. coated fibers in			Contralateral radiological abnormalities
					Duration (years)	Latency period (years)	Sputum	BALF (ml)	Dried lung (gm)	
Steam-fitter's wife	8	F	57	E	30	30		2		+
Secretary in rubbish chute factory	9	F	45	E	20	20		2.7		+
Power-plant operator	10	M	51	E	26	26		0.2	1,040	+
Railway joiner	11	M	72	E	33	40	3			+
Railway maintenance worker	12	M	68	E	30	43		1.6		-
Aluminum furnaceman	13	M	58	M	25	25		0.8	2,000	-
Jeweller	14	M	89	E	31	40		0.2	60,000	+
Electronic fitter (medical equipment)	15	M	76	F	50	60			2,400	+
Chemical factory mason	16	M	74	E	23	31		2.1		+
Station maintenance worker	17	M	62	E	35	44		2.2	1,000	+

Key words: E = epithelial, M = mixed, F = fusiform, BALF = bronchoalveolar lavage fluid.

TABLE III. Clinical and Microscopical Features in Ten Cases Without Past Asbestos Exposure

Occupation	No.	Sex	Age	Histological type	No. coated fibers in sputum	BALF (ml)	Dried lung (gm)	Contralateral radiological abnormalities
Leather goods maker	27	M	75	E	0		6.903	-
Literature teacher	28	M	57	E	0			-
Printer (silk screen process)	29	M	56	E	0			-
Clerk	30	F	56	E				+
Clerk	31	F	45	E			39	-
Lamp bulb inspector	32	F	59	E	0			-
Glass inspector	33	F	64	F		0.15		-
Typesetter	34	M	41	E				-
Mail sorting clerk	35	M	67	E				-
Working proprietor	36	M	48	E				-

Key words: E = epithelial, BALF = bronchoalveolar lavage fluid.

TABLE IV. Clinical and Microscopical Features in Nine Inconclusive Questionnaire Cases

Occupation	No.	Sex	Age	Histological type	No. coated fibers in sputum	BALF (ml)	Dried lung (gm)	Contralateral radiological abnormalities
Ironer	18	F	68	E				-
Jeweller's daughter	19	F	35	E				-
Automobile mechanic's wife	20	F	68	M			560	+
Resident opposite asbestos-sprayed building	21	F	73	E		0.7		+
Bookkeeper in asbestos-sprayed room	22	F	67	E		2.3		-
Lathe operator/coil winder	23	M	71	E			93,600	+
Automobile mechanic	24	M	70	E		0		-
Constructional steel erector	25	M	70	E		1	2,000	+
Vehicle upholsterer	26	M	64	E		0.9		-

Key words: E = epithelial, M = mixed, BALF = bronchoalveolar lavage fluid.

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TABLE V. Clinical, Histological, Radiological, and Biological Features in 27 Mesotheliomas With Conclusive Questionnaires

Parameters	Asbestos-exposed cases (questionnaire +) (n = 17)	Nonasbestos-exposed cases (questionnaire -) (n = 10)	p Value
Mean age (years)	64.1 ± 10.7	56.8 ± 10.3	NS
Mean survival time (months)	11.9 ± 4.6	31 ± 12.6	< 0.01
PPD test (diameter mm)	5.3	12.2	< 0.05
Contralateral radiological abnormalities (percentage)	76	10	< 0.001
Males (percentage)	88	60	NS
Histological type (percentage)			
Epithelial	70	100	NS
Fusiform	12		
Mixed	18		
Open thoracotomy (percentage)	35	50	NS

DISCUSSION

If we consider only the cases for which an asbestos exposure has been assessed on the basis of the questionnaire, the percentage of exposed cases (47%) is very low in comparison with the percentage found by others (72% for Planteydt [1979], 68% for Greenberg et al [1974], 66% and 72% for McDonald [1979] and McDonald and McDonald [1980] in Canada and in USA, respectively, and 77% for Bignon et al [1979b] in the French national mesothelioma register). We have previously validated the interest of measurement of coated and uncoated fibers in pulmonary biological specimens [Bignon et al, 1979a]. The use of both methods, questionnaire and measurement led to a better assessment of past asbestos exposure [Di Menza et al, 1980]. Using these two methods, we found 6 additional cases in the 9 inconclusive questionnaire cases and 3 other exposed cases in the 10 negative questionnaire cases. One of these cases (case 27) was a leather goods maker, who probably had been exposed to asbestos in the past. (A mesothelioma case has been described in shoemakers [Decoufle, 1980].) We have observed two cases with atypical asbestos exposures. The first one was a farmer who constructed hen houses using asbestos cement several years ago. A case with similar exposure has been published by Ashcroft [1973]. The second one was a jeweller, an occupation already noted in the case published by Cochrane and Webster [1978]. The asbestos exposure was occupational in males, but household and paraoccupational exposures were noticed in females. This sex-related type of exposure has been already noted [Hasan et al, 1977; Vianna and Polan, 1978; McDonald, 1979]. Our findings concerning the length of the asbestos exposure, the latency period, the mean age, the sex ratio, and the pleural or peritoneal localization are similar to the data previously published [Seikoff, 1976; Greenberg and Lloyd Davies, 1974; Hinds, 1978; Planteydt, 1979; McDonald, 1979].

A great number of agents, when introduced experimentally into pleural or peritoneal cavities, may induce pleural or peritoneal tumors. In that regard, mesotheliomas have been induced in animals with glass fibers and glass powder [Wagner et al, 1973], aldehyde wood lignin constituents [Schoental and Gibbard, 1972], 1-nitroso-5,6-didouracile [Pelfrene and Garcia, 1975], sterigmatocystin [Terao, 1978], methyl

(acetoxyethyl) nitrosamine [Berman and Rice, 1979], and herbicides [Donna et al, 1980]. On the other hand, several agents have been shown to have a synergistic carcinogenic effect with asbestos: irradiation [Lafuma et al, 1980], irradiation and 3-methylcholanthrene [Warren et al, 1981], N-methyl-N-nitrosourea [Kawai, 1979], and dimethyl benz(a)anthracene [Topping and Nettekheim, 1980]. The complete work histories of the nonasbestos exposed cases (Table III) point out some hypothetical etiological factors that have to be discussed in regards to these experimental data. Two patients (cases 32 and 33) have been exposed to glass dust during the destruction of mishapen lamp bulbs or glasses. One patient (case 28) was a white-collar worker who presented with a radiological opacity in the right costophrenic angle and who had been systematically X-rayed in that region (cumulative exposure of 9.5 rads over 26 years) and who developed a mesothelioma at the same place. This resembles a case one of us (J. Bignon) observed after collapse therapy for pulmonary tuberculosis [Chretien et al, 1968]. Another patient (case 29) used melted paraffin. This finding must be compared to a recent case of pleural mesothelioma developed in close contact to a paraffin lung granuloma in a subject regularly ingesting paraffin oil [Meyniard et al, 1980].

The group of cases without asbestos exposure showed several features significantly different from those of the asbestos-exposed group, particularly if we consider the case no. 27 to have been exposed in the past according to the great number of coated fibers found in the lung (Table III). Among those features, age and sex ratio are in close analogy to the observations made by Peto et al [1981] in the cases where no asbestos exposure was reported among mesothelioma diagnosed in Los Angeles County: (1) The nonexposed subjects were younger (almost 10 years) than the exposed subjects. (2) A similar incidence in men (6 cases) and women (4 cases) was observed in the unexposed group contrasting with a male predominance in the exposed group. Peto et al [1981, 1982] found that for exposed cases, the mesothelioma rate was related to time since first exposure, while for unexposed cases the rate was related to age. This suggests that the "unexposed" cases may be due either to an environmental exposure to fibers from childhood, as seems to be the case in Turkey [Saracci et al, 1982] or to another agent. However, in our study no etiological factor has been discovered. It could be also a natural disease! Elsewhere, in these series, other discrepancies have been noted: (3) The contralateral asbestos-related radiological signs were present in 13 out of the 17 asbestos-exposed cases and absent in 9 out of the 10 unexposed cases. (4) In the 17 asbestos-exposed cases, mesotheliomas were of epithelial type in 12 cases, mixed in 3, and fusiform in 2. In the 10 cases without past asbestos exposure, mesotheliomas were exclusively of epithelial type. Peto et al [1981] suggested that such cases could not be mesothelioma at all! However, in our cases, there was a total agreement of the mesothelioma panel. (5) The survival time after diagnosis of the unexposed cases was significantly longer (by a factor of two) than that of the exposed; we have no explanation for this difference.

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*Since the proofing of this paper, we observed two additional cases without definite asbestos exposure: one is the sister of case no. 36 (Table III), 44 years old, who worked as a philosophy teacher. The two siblings spent their childhood in the vicinity of a dirty plant making glue. The other case is a man, 57 years old, military, who lived from birth to 19 years in the neighborhood (less than 500 meters) of the Gironde shipyard.

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asbestos exposure: one patient. The two siblings were 57 years old, military service in the Gironde shipyard.

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