Eur. J. Oncol., vol. 13, n. 3, pp. 181-186, 2008

Familial mesothelioma: a puzzling issue

Mesotelioma familiare: una questione enigmatica

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Summary

***Aim*. The present study was conducted to collect data about familial mesothelioma, an occurrence once considered as exceptional and now reported with increasing frequency. *Patients and methods*. Eight cases of familial pleural mesothelioma were identified in various areas of Italy (the Tuscany Region and the Monfalcone district). The diagnosis was based on histological examination in six cases, and confirmed by necropsy in two of them. Occupational and social histories were obtained from the patients themselves or from their relatives by means of personal interviews. Asbestos bodies were isolated from the lung in the two necropsy cases, following the Smith and Naylor method. *Results*. The group included six men and two women, aged between 47 and 88 years. There were one couple father-son, one couple mother-daughter, one couple of brothers, and one couple of cousins. The male patients had been exposed occupationally to asbestos in various industries. The two women had histories of asbestos exposure at home, their husband-father having worked in a foundry. The latency periods (time intervals between first exposure to asbestos and diagnosis of the tumour) ranged between 34 and 56 years. Lung asbestos bodies isolated in the**

Riassunto

***Finalità*. Il presente studio è stato condotto per raccogliere dati sul mesotelioma familiare, un'evenienza un tempo considerata eccezionale e ora riferita con crescente frequenza. *Pazienti e metodi*. Otto casi di mesotelioma familiare della pleura sono stati identificati in varie parti d'Italia (nella Regione Toscana e nell'area di Monfalcone). La diagnosi era basata su reperti istologici in sei casi e confermata anche dall'autopsia in due di questi. Le storie professionali e sociali sono state ottenute dal paziente stesso o dai suoi parenti attraverso interviste personali. Nei due casi autoptici sono stati isolati i corpi dell'asbesto dal tessuto polmonare secondo il metodo Smith-Naylor. *Risultati*. Il gruppo era costituito da sei uomini e due donne, di età variabile tra 47 e 88 anni. La relazione di parentela nelle quattro coppie era padre-figlio, madre-figlia, due fratelli e due cugini. I pazienti maschi avevano subito un'esposizione professionale all'asbesto in varie industrie. Le due donne avevano una storia di esposizione domestica all'asbesto, in quanto il loro marito-padre aveva lavorato in una fonderia. Il periodo di latenza (intervallo di tempo intercorso tra prima esposizione all'asbesto e diagnosi del tumore) variava tra 34 e 56 anni. I corpi dell'asbesto isolati**

Received/Pervenuto 26.5.2008 - Accepted/Accettato 5.6.2008
Address/Indirizzo: Prof. Claudio Bianchi, Centre for the Study of Environmental Cancer, Italian League against Cancer, Hospital of Monfalcone, 34074 Monfalcone (GO), Italia - Tel. +39/0481/44007 - Fax +39/0481/487677 - E-mail: legatumori1@interfree.it

couple father-son were 55,000 and 169,000 per gram of dried tissue. *Conclusions*. In accordance with other studies, the present findings indicate that familiarity is not an alternative aetiologic explanation to asbestos. In their natural history, familial cases do not seem to differ from the sporadic ones. It remains doubtful whether mesothelioma among blood-related subjects may or may not indicate a genetic-based susceptibility to mesothelioma. Eur. J. Oncol., 13 (3), 181-186, 2008

Key words: **mesothelioma, pleura, familial cancer, occupational cancer, asbestos**

nella coppia padre-figlio erano 55.000 e 169.000 per grammo di tessuto secco. *Conclusioni*. In accordo con altri studi, i presenti risultati mostrano che la familiarità non rappresenta una spiegazione eziologica alternativa all'asbesto. La storia naturale dei mesoteliomi familiari non sembra differire da quella dei casi sporadici. Rimane dubbio se il mesotelioma in persone consanguinee indichi o meno una suscettibilità su base genetica nei confronti del tumore. Eur. J. Oncol., 13 (3), 181-186, 2008

Parole chiave: **mesotelioma, pleura, tumori familiari, tumori professionali, asbesto**

Introduction

The occurrence of mesotheliomas in several members of the same family has been reported since the pivotal study of Wagner *et al*, in 1960[1]. The series of 33 pleural mesotheliomas described by these researchers included a couple father-daughter. The father, who had a diagnosis of mesothelioma at the age of 68 years, had spent his whole life in the vicinity of the mines; in addition he had been a miner for long periods. The daughter, diagnosed with mesothelioma at 42 years of age, had lived in the vicinity of the mine until the age of 20.

A number of papers have been published on this issue after that date[2-5]. The question is clear: does the development of mesothelioma in blood-related subjects of a family indicate a genetic-based susceptibility?

The question is of great importance. Asbestos is certainly the cause of mesothelioma in nearly 100% of the cases[6-7]. However, the fact that only a relatively small proportion of people severely exposed to asbestos develop mesothelioma indicates that cofactors play a rôle[8]. Such factors remain to be identified, with genetic susceptibility being a major candidate.

In the present study we reviewed eight cases of pleural mesothelioma, seen in four families in different areas of Italy.

Patients and methods

Six cases were identified within the framework of the activity of the Mesothelioma Registry in the Tuscany Region; a further two cases were encountered in the course of a study on familial mesothelioma in Monfalcone. The diagnosis was based on histological examination in six cases, on cytological findings in one case, and on clinical data in one. Occupational and social histories were obtained from the patients themselves or from their relatives by means of personal interviews. In two cases, examined at necropsy, asbestos bodies were isolated from the lung tissue and counted, following the Smith-Naylor method[9].

Results

The group included six men and two women, aged between 47 and 88 years (mean 69.1 years). The degrees of kinship varied (Table 1). All the male patients had histories of occupational exposure to asbestos, having worked in various industries. The two women had probably been exposed at home, their husband-father having worked in the production of ferrochromium alloys in a factory largely insulated with asbestos. Latency periods, defined as time intervals between first exposure to asbestos and

Table 1 - Familial mesothelioma of the pleura: main features in 8 cases

Family N.	Case N.	Sex	Age	Residence place	D[a]	Incidence year	Relation	Asbestos exposure	Latency period (years)
1	1	M	69	Monfalcone	A[b]	1981	Father	Shipyards, sheet metal worker	54
	2	M	67	Monfalcone	A	2005	Son	Shipyards, electrician	48
2	3	F	82	Massa	B[c]	2003	Mother	Domestic exposure	38 (?)
	4	F	47	Spezia Province	Cl[d]	1999	Daughter	Domestic exposure	34 (?)
3	5	M	79	Leghorn	B	1995	Brother	Petrochemical industry maintenance worker	45
	6	M	88	Leghorn	Cyt[e]	2002	Brother	Shipyards, welder	56
4	7	M	61	Prato	B	1988	Cousin	Rag sorter	52
	8	M	60	Prato	B	1996	Cousin	Rag sorter	46

[a] D = diagnosis
[b] A = autopsy
[c] B = biopsy
[d] Cl = clinical
[e] Cyt = cytology

diagnosis of the tumour, ranged between 34 and 56 years. The burdens of lung asbestos bodies isolated in the couple father-son (cases 1 and 2), were 55,000 and 169,000 bodies per gram of dried tissue, respectively. Both the patients showed large pleural plaques at necropsy. An exemplar case is presented in figs. 1-2.

Discussion

The abundant literature on familial mesothelioma is not easy to evaluate. In a large majority of papers, such as the present one, only some cases are described, without any reference to a denominator. However, in some studies a denominator is reported.

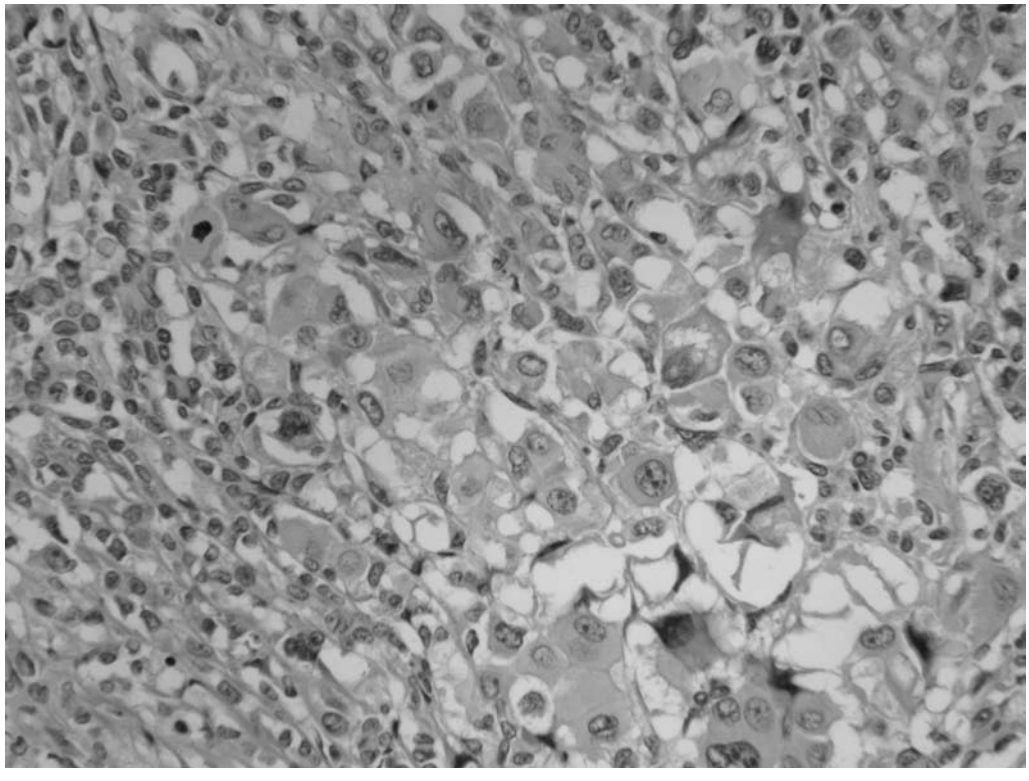

Fig. 1. Case 2. Pleural mesothelioma with large anaplastic cells
Epithelial and sarcomatous patterns were visible in other parts of the tumour
H-E, 400x

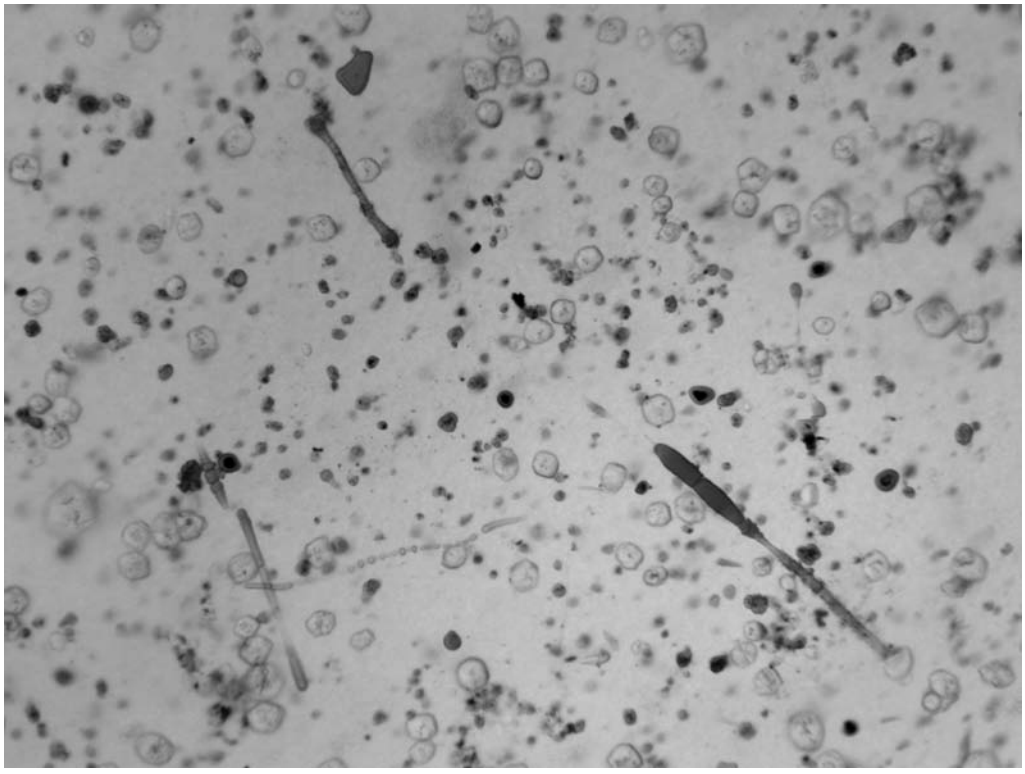

Fig. 2. Case 2. Asbestos bodies isolated after chemical digestion of lung tissue 400x

By investigating a series of 610 pleural mesotheliomas in the Trieste-Monfalcone area, Italy, 40 cases of familial mesothelioma were identified[2]. All the familial cases but three belonged to the original series of 610 mesotheliomas. The cases affecting blood-related subjects were 31, and 25 by excluding those couples in which only one of the two members had been comprised in the original series. This corresponds to a percentage of familial cases with blood relationship of 3.8%, a proportion not negligible for a tumour that remains rare even among people heavily exposed to asbestos. All the cases of the Trieste-Monfalcone series have histories, and mostly also objective signs, of exposure to asbestos. However, the age distribution and duration of the latency period in the familial cases did not differ from the sporadic ones, a fact speaking against a possible rôle of genetic factors[2].

By examining the data collected by three Italian Mesothelioma Registries, Ascoli *et al*[3] found 22 blood-related familial cases in a series of 1,954 pleural mesotheliomas.

In some mesothelioma case series, a relatively high prevalence of patients with family history of mesothelioma have been observed. In a group of 100 malignant pleural mesotheliomas, investigated at the Egyptian National Cancer Institute in Cairo, Gaafar and Aly Eldin[10] observed seven cases with a family history of mesothelioma. The degree of kinship is not specified. A majority of patients in this series had histories of environmental exposure to asbestos. In a recent study on malignant pleural mesothelioma in a rural Turkish population with environmental exposure to asbestos, Metintas *et al*[11] studied 131 patients. Five of these had a family history of mesothelioma.

The available data on familial mesothelioma show that asbestos is nearly constantly involved. In the current series, three people had worked in the shipyards, one in the petrochemical industry, and two as rag sorters in the textile industry. The family member of cases 3 and 4 had worked in a foundry. Asbestos exposure in such branches of industry has been widely investigated[12-16]. The risks related to domestic exposure to asbestos are also well known[17-20]. Therefore, familiarity does not represent an alternative aetiologic explanation to asbestos. However, the meaning of familial aggregation of mesothelioma cases remains difficult to define. Recently, Ugolini *et al*[21] analyzed the literature on familial mesothelioma. The Family History Score Z_i

was used to determine whether familial clusters of mesothelioma might be attributed or not to random occurrence. According to the researchers, the hypothesis of chance occurrence may be rejected on the basis of the test they used. However, if a familial factor plays a rôle in the genesis of mesothelioma, this factor is not necessarily identifiable with genetic susceptibility.

Some perplexity on the rôle of genetic predisposition remains for several reasons. Firstly, among familial cases in the literature, often heavy and very heavy exposures to asbestos were the cause. For instance, a long history of work in insulation does account alone for the development of mesothelioma. Secondly, familial occurrence of mesothelioma is rather frequent in situations of environmental exposures to asbestos[10, 11]. Such a type of exposure mostly begins at birth, giving an opportunity to all of the family members to experience a similar exposure for decades. In particular, several mesotheliomas have been reported in unusual settings, such that of a family living inside an asbestos-cement factory[22], or that of a family producing asbestos-cement in their home[23]. These people shared a long and heavy exposure to asbestos and this seems to be a more adequate explanation than genetics for these cases. Finally, it should be emphasized that familial mesothelioma comprises, besides the cases among blood-related subjects, also cases developing among persons without blood relationships[2]. These cases suggest the possible rôle of a variety of conditions, which family members generally share.

In conclusion, familial mesothelioma seems not to be an exceptional occurrence. Its meaning remains uncertain.

Acknowledgements

This study has been supported by a grant from the Cassa di Risparmio di Gorizia Foundation, Gorizia, Italy.

References

1. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the north western Cape Province. Br J Ind Med 1960; 17: 260-71.
2. Bianchi C, Brollo A, Ramani L, *et al*. Familial mesothelioma of the pleura. A report of 40 cases. Ind Health 2004; 42: 235-9.
3. Ascoli V, Cavone D, Merler E, *et al*. Mesothelioma in blood related subjects: report of 11 clusters among 1954 Italy cases and review of the literature. Am J Ind Med 2007; 50: 357-69.
4. Wilkins A, Popat S, Hughes S, *et al*. Malignant pleural mesothelioma: two cases in first degree relatives. Lung Cancer 2007; 57: 407-9.
5. You B, Blandin S, Gérinière L, *et al*. Family mesotheliomas: genetic interaction with environmental carcinogenic exposure? Bull Cancer 2007; 94: 705-10 (in French).
6. Bianchi C, Bianchi T. Malignant mesothelioma: global incidence and relationship with asbestos. Ind Health 2007; 45: 379-87.
7. Bianchi C, Bianchi T, Tommasi M. Mesothelioma of the pleura in the Province of Trieste. Med Lav 2007; 98: 374-80 (in Italian).
8. Giarelli L, Bianchi C. Host factors in asbestos-related mesothelioma. Eur J Oncol 1999; 4: 541-3.
9. Smith NJ, Naylor B. A method for extracting ferruginous bodies from sputum and pulmonary tissue. Am J Clin Pathol 1972; 58: 250-4.
10. Gaafar RM, Aly Eldin NH. Epidemic of mesothelioma in Egypt. Lung Cancer 2005; 49 suppl 1: S17-S20.
11. Metintas M, Metintas S, Ak G, *et al*. Epidemiology of pleural mesothelioma in a population with non-occupational asbestos exposure. Respirology 2008; 13: 117-21.
12. Bianchi C, Brollo A, Ramani L. Asbestos exposure in a shipyard area, Northeastern Italy. Ind Health 2000; 38: 301-8.
13. Bianchi C, Brollo A, Ramani L, *et al*. Asbestos exposure in malignant mesothelioma of the pleura: a survey of 557 cases. Ind Health 2001; 39: 161-7.
14. Gennaro V, Finkelstein MM, Ceppi M, *et al*. Mesothelioma and lung tumors attributable to asbestos among petroleum workers. Am J Ind Med 2000; 37: 275-82.
15. Paci E, Dini S, Buiatti E, *et al*. Malignant mesothelioma in non-asbestos textile workers in Florence. Am J Ind Med 1987; 11: 249-54.
16. Bianchi C, Bianchi T. Amianto. Un secolo di sperimentazione sull'uomo. Trieste: Hammerle Editori, 2002.
17. Anderson HA, Lilis R, Daum SM, *et al*. Asbestosis among household contacts of asbestos factory workers. Ann N Y Sci 1979; 330: 387-99.
18. Dodoli D, Del Nevo M, Fiumalbi C, *et al*. Environmental household exposure to asbestos and occurrence of pleural mesothelioma. Am J Ind Med 1992; 21: 681-7.
19. Bianchi C, Bianchi T, Ramani L. Malignant mesothelioma of the pleura among women. Med Lav 2004; 95: 376-80 (in Italian).
20. Miller A. Mesothelioma in household members of asbestos-exposed workers: 32 United States cases since 1990. Am J Ind Med 2005; 47: 458-62.

21. Ugolini D, Neri M, Ceppi M, *et al*. Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. Mutat Res 2008; 658: 162-71.
22. Giuliani F, Galetta D, Colucci G. Mesotelioma pleurico: contaminazione con asbesto di un nucleo familiare. Eur J Oncol 1999; 4: 399-401.
23. Otte KE, Sigsgaard TI, Kjærulff J. Malignant mesothelioma: clustering in a family producing asbestos cement in their home. Br J Ind Med 1990; 47: 10-3.