EXPOSURE TO ASBESTOS AND LUNG CANCER: A CASE REPORT.

ESPOSIZIONE AD AMIANTO E NEOPLASIA POLMONARE: CASE REPORT.

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Abstract

In Greek αμίαντος (asbestos) means immaculate and incorruptible and ἀσβηστος (asbestos) perpetual and inextinguishable. The knowledge of its particular characteristics and its applications dates back to ancient times, for example, Egyptians already used it for embalming.

Industrial use of asbestos dates back to the late nineteenth century, following the discovery of large Canadian deposits in Quebec (1877). The later discovery of important deposits in South Africa (crocidolite, chrysotile, amosite), Russia (chrysotile), United States (chrysotile), Australia (crocidolite) and Finland (anthophyllite), Italy (chrysotile) favoured its spreading and use on a large scale.

Asbestos has been a well known confirmed human carcinogen since 1992, but before that date it was widely and regularly used for its insulating properties and its resistance. Exposure to asbestos appears associated to several diseases, such as pulmonary fibrosis, asbestosis (characterized by typical lung lesions), and neoplasms such as pleural and peritoneal mesothelioma and pulmonary adenocarcinoma. To put the blame of a disease on exposure to asbestos, however, diagnostic criteria are needed, ranging from the discovery of asbestos fibers in lung parenchyma to an array of radio-immuno-histo-chemical findings, to the duration and extent of exposure, etc. Here is a case report of lung cancer attributed to exposure to asbestos, which reconstructs the history of the patient in a critical analysis of the diagnostic criteria. Data have been discussed in the light of the current knowledge, with the support of a scrupulous literary review, which lead us step by step along the evolution of our achievement about the carcinogenicity of asbestos. Mr P (1932-2002) worked for a transport tramway company at the routine maintenance and repairs and died for lung adenocarcinoma. Scientific information worldwide produced about asbestos and its effects on human health are abundant, but it can't be assumed that what is now universally recognized and taken for granted was recognized and taken for granted and with the same diffusion in past years and in the years during which Mr. P worked (1955-1992). Hence, there is no certainty of the diagnosis of the lung primitive adenocarcinoma attributed to Mr. P because the diagnostic criteria suggested by the international literature have not been strictly applied. There are no clinical or instrumental or laboratory signs that can be considered as indicators of the effect of exposure to asbestos: pulmonary fibrosis, asbestosis, pleural plaques, asbestos fibers, asbestos corpuscles, and the hypotesis of a possible cause and effect relationship is not supported by valid data.

🇮🇹 Abstract

In greco la parola amianto significa immacolato e incorruttibile e asbesto perpetuo ed inestinguibile. La conoscenza delle sue particolari caratteristiche e l'utilizzo risalgono a tempi antichissimi, ad esempio già gli Egizi lo utilizzavano per l'imbalsamazione.

L'impiego industriale dell'amianto risale agli ultimi decenni dell'Ottocento in seguito alla scoperta dei vasti giacimenti canadesi del Quebec (1877). La successiva scoperta d'importanti giacimenti anche in Sudafrica (crocidolite, crisotilo, amosite), Russia (crisotilo), Stati Uniti (crisotilo), Australia (crocidolite) e Finlandia (antofillite), Italia (crisotilo) ne favorì la diffusione e l'uso su vasta scala. L'amianto è un noto cancerogeno riconosciuto dal 1992, ma prima di questa data veniva ampiamente e regolarmente utilizzato per le sue proprietà isolanti e di resistenza. L'esposizione ad asbesto risulta correlata a diverse patologie, quali fibrosi polmonare, asbestosi (caratterizzata da lesioni polmonari tipiche), e neoplasie quali mesotelioma pleurico e peritoneale ed adenocarcinoma polmonare. Per attribuire una patologia all'esposizione ad amianto però occorrono dei criteri diagnostici, che vanno dal ritrovamento delle fibre di asbesto nel parenchima polmonare ad una batteria di reperti radio-immuno-isto-chimici, alla durata ed all'entità dell'esposizione, etc. Riportiamo un case report di neoplasia polmonare attribuita ad esposizione ad amianto, in cui viene ricostruita la storia del paziente in un'analisi critica dei criteri diagnostici. I dati vengono ridiscussi alla luce delle conoscenze attuali, con il supporto di una review della letteratura che ci accompagna attraverso l'evoluzione delle conoscenze concernenti la cancerogenicità dell'amianto. Il Sig. P nato nel 1932 e deceduto nel 2002 per adenocarcinoma polmonare, ha lavorato occupandosi della manutenzione ordinaria e straordinaria di mezzi tramviari aziendali. Le informazioni scientifiche che sono state prodotte in tutto il mondo sull'amianto/asbesto ed effetti sulla salute umana sono copiose, ma non si può

ritenere che quanto oggi è scontato ed universalmente riconosciuto lo fosse anche negli anni passati e con la stessa diffusione di oggi e negli anni durante i quali il Sig. P ha prestato servizio, per cui non è stato possibile chiarire con certezza l'eziologia della malattia. Non vi è quindi certezza della diagnosi di adenocarcinoma primitivo del polmone attribuito al Sig. P in quanto non sono stati applicati rigorosamente i criteri diagnostici suggeriti dalla letteratura internazionale. Non risultano segni clinici, strumentali o di laboratorio che possano essere presi in considerazione come indicatori di effetto di esposizione ad amianto: fibrosi polmonare, asbestosi, placche pleuriche, fibre di amianto, corpuscoli di asbesto, e l'ipotesi di un' eventuale relazione causa ed effetto non è supportata da dati validi.

Background

In Greek αμίαντος (asbestos) means immaculate and incorruptible and ἀσβηστος (asbestos) perpetual and inextinguishable. The knowledge of its particular characteristics and its applications dates back to ancient times, for example, Egyptians already used it for embalming.

Industrial use of asbestos dates back to the late nineteenth century, following the discovery of large Canadian deposits in Quebec (1877). The later discovery of important deposits in South Africa (crocidolite, chrysotile, amosite), Russia (chrysotile), United States (chrysotile), Australia (crocidolite) and Finland (anthophyllite), Italy (chrysotile) favoured its spreading and use on a large scale. Actinolite and tremolite are considered little commercial relevance pollutants.

Until 1930, relatively small amounts of asbestos have been used (338,783 tonnes in 1930), but quantities have gradually increased over the following decades until reaching 5.159.000 tons in 1978.

In 1969, Canada supplied 45.9% of the world production. USSR followed with 26.8%, South Africa with 7.9%, China with 5%, other countries followed with minor shares.

The physico-chemical properties of asbestos and its intrinsic properties - nonconducting, insulating, anti-vibration, spinnable in fabric and fire retardant material - have facilitated its use in many fields of production and have led to an extensive use. Here its application fields:

-Construction: asbestos-cement slabs (Eternit), tiles, pipes, decoration, fire retardant panels, spray application for
  insulating plasters;
-Shipbuilding industry: insulating and fire-fighting coatings;
-Aviation industry: insulating and fire-fighting coatings;
-Railway industry: insulating and fire-fighting coatings;
-Automotive industry: brake and friction linings, insulating applications;
-Plastics industry: additives, various artifacts reinforcing;
-Chemical industry: filter and gaskets for various functions, thermosetting and thermoplastic resins;
-Metal Industry: guards and protective clothing, insulators for furnaces, boilers, etc.;
-Asbestos textile industry: textiles, tapes, ropes, twines, yarns, upholstery;
-Other: coveralls and protective fire or heat resistant clothing, papers, cardboards, electrical insulators, paints, talc.

This material was widely used for its characteristics of technical utility until the time of its ban that dates back to 1992.

Scientific information worldwide produced about asbestos and its effects on human health are abundant, but it can't be assumed that what is now universally recognized and taken for granted was recognized and taken for granted and with the same diffusion in past years and in the years during which Mr. P worked (1955-1992).

Analysis of literature data, including the most recent, allows us to provide an updated overview on the subject; we thought it essential to plot the over time numerical trend of publications of international literature on health effects of asbestos exposure.

The number of censused papers is less than ten until 1964, about one hundred from 1972 to 74, about 150 until 1978. Since 1982 there has been a growing interest and with an average production per year of about 350 scientific papers. There are two peaks in 1982 and 2001 respectively with 430 and 562 publications.

In these works effects on human health due to exposure to asbestos are identified and defined:

-Diffuse interstitial fibrosis or parenchymal asbestosis;
-Non-malignant pleural diseases or pleural asbestosis (thickening, plaque effusions);
-Hands and forearms skin lesions (warts);
-Asbestos related cancer disease (mesothelioma, lung cancer).

Case Report

Mr. P (1932-2002) died for lung adenocarcinoma, worked for a transport tramway company at the routine maintenance and repairs. Mr. P was hospitalized in April 2001, with a history of hypertension since the age of 52 associated with ischemic heart disease; he had had night dyspnea for 6 months with sudden awakenings; former smoker, 20 cigarettes/day since he was young, he had given up smoking when 50. A Chest radiography performed during hospitalization showed "round opacity in right field." He underwent bronchoscopy in the apical segment of the lower lobe that pointed out modest extrinsic compression of about 2 mm from the apex where thickened and whitish mucosa appeared. The tumor markers were "negative." Sputum cytological examination revealed: "material consisting of numerous neutrophils and some squamous epithelial cells exempt from significant atypia". He performed T.A.C. total body revealing: " negative skull; a round solid formation with inhomogeneous enhancement with diameter of about 8 cm between the posterior segment of the upper lobe and the apical segment of the lower right lobe of the lung. Costal pleura is involved with loculated pleural effusion. Two nodular tumefactions related to the pulmonary veins lymph nodes. Upper abdomen negative". Lung biopsy with needle aspiration revealed: "Using ultrasound guidance we proceed to needle aspiration for cytological examination (SIC) of the parenchymal tumefaction located at the right lung." The discharge diagnosis was "adenocarcinoma of the lower lobe of the right lung on transthoracic needle biopsy. Ischemic heart disease ". No mention of cytological examination report.

The patient was hospitalized again in December 2001. Pulmonary function tests revealed a ventilatory insufficiency of obstructive type. Chest radiography showed "opacity with irregular margins in the apical segment of the lower right lobe, striae of connection with the hilum with retraction of the area; stapling of the right diaphragmatic pleura, prominent hilum, not active pleural effusions. Mr. P was therefore subjected to an intervention for right pneumonectomy. A standard chest radiography performed after surgery showed "outcomes of right pneumonectomy with leveled residual cavity, no left pleuroparenchimal injury; right pleural drainage." The patient was discharged in December 2001 in good condition, and in the documentation of hospitalization there was no mention of the histological examination on removed lung.

In August 2002, the patient underwent a new hospitalization for metastatic lung cancer: "Liver metastases. Episode of atrial fibrillation. Pericardial effusion. Suspected metastases of soft tissue on right supraclavicular region and dyspnea." T.C. total body showed "skull negative; chest: results of right pneumonectomy, pericardial effusion, no alteration in the left lung; abdomen showed 22 mm hepatic nodule hypothesis of injury repetitive, 16 mm retro peritoneal nodule." Echo-color-doppler-rate showed an EF 40% and moderate pericardial effusion.

Discussion

In order to realize whether the cause of his death could be an occupational disease, we analyzed the data in our possession, drawing some considerations.

1. Diagnostic certainty of neoplastic disease:

Here are the salient data obtained from the clinical documentation. Actually in medicine there are quality criteria that must be met when talking of lung cancer diagnosis which in this case have not even been considered.

It is clear that the diagnosis of adenocarcinoma is said to come from an initial examination defined cytologic but the report is missing. Cytological examination is known, to be an investigation with many limitations and possibilities of error. We read in the record, "histological examination: poorly differentiated adenocarcinoma of the lung" but no proof is present, so that it is legitimate to wonder if the words cytological examination stand for histological examination by needle aspiration. However, even if it were a histological examination, the reporting of an examination of this type should present indications about the amount of material taken, the type of staining and fixatives used, the centrifugation, the storage etc. And there's still the difficulty of distinguishing the histotype of a tumor which is then defined as poorly differentiated, but without objective data to be used as criteria. The table shows the classification of histological types of adenocarcinoma with molecular characteristics.

Table 1. *Classification of histological types of adenocarcinoma with molecular characteristics.*

Molecular characteristics	EGFR	KRAS	EML4/ALK
Hystology	Invasive adenocarcinoma + adenocarcinoma in situ	Adenocarcinoma	Adenocarcinoma
Subtype	Non-mucinous	Non-mucinous	Mucinous (goblet cells)
TC characteristics	Mixed GGO / solid or solid	Mixed or solid	Solid
TTF-1	+	-	+
Smoke exposure	Non smoker	smoker	Non smoker
Ethnicity	east Asia		All
Gender	Females> Males	Males> Females	Males> Females

Abbreviations: EGFR, epidermal growth factor receptor; EML4/ALK, echinoderm microtubule-associated protein-like 4 gene and anaplastic lymphoma kinase gene;TC, computerized tomography; GGO, ground glass opacity; TTF-1, thyroid transcription factor-1; TKI, tyrosine kinase inhibitor.

For cancers that require cytological and histological examination it is also important to choose the fragment/s to be examined (1).

One possible source of error may be due to the analysis of a fragment, not representative of the disease. This is clear from the study by Nigrisoli (2). He examined 1490 samples at the cryostat, and found that the causes of failure are mainly due to errors of macroscopic sampling and secondly to a misunderstanding of the histological examination. These factors may explain the poor diagnostic accuracy (3).

If histological examination had shown a suspicion of primitive adenocarcinoma, this tumor should have to be distinguished from a metastasis of adenocarcinoma with a different source, -eg colon or rectum through immuno-histochemical investigations at least. Regarding to immunohistochemistry offers the pathologist the opportunity to increase the rate of diagnostic accuracy, especially in the cases of biopsy representative of poorly differentiated neoplasms (4, 5), above all when it comes to needle aspiration exam which is also less accurate than histological examination on biopsy.

In cases of poorly differentiated lung carcinoma, a panel of immunophenotypic characterization of first line could allow to lean towards a particular and specific histotype.

Notwithstanding rare exceptions the coexpression of cytokeratin 7 and thyroid transcription antigen factor-1 (TTF-1), together with the negativity for cytokeratin 20, cytokeratin 5/6, high molecular weight cytokeratins and for p63, might allow to facilitate a diagnosis of adenocarcinoma (6, 7). According to Tsuta (8), the combination of cytokeratin 5/6 and TTF-1 is the most valid immunohistochemical combination for the diagnosis of a lung adenocarcinoma.

Many authors (8, 9, 10, 11, 12) argue that the tumor immunohistochemical characterization is important for a differential diagnosis. According to Turner (2012) the analysis of immuno-histochemical markers is essential for the differential diagnosis between adenocarcinoma and other types of cancers, pulmonary, non-pulmonary and metastatic (13). According to Ye (14, 15) and many authors (16, 17, 18) the study of immunohistochemical markers is useful to distinguish primary lung adenocarcinoma from adenocarcinoma of other sites that has metastasized in the lung, especially in cases of poorly differentiated adenocarcinoma (18). According to Saleh (19) immunocytochemical investigations have a significant role in the differential diagnosis between adenocarcinoma and metastasis.

Other clinical tests, such as lower abdomen CT, useful to exclude the presence of primary tumors in other locations, were not performed.

It is well know that:

a. the diagnosis must be made on the autoptic workpiece in the presence of different samples to differentiate the lung carcinoma from a possible other cancer or a secondary tumor that has metastasized to the lung;

b. in the presence of surgical specimen the immunohistochemical investigations are also useful to support a differential diagnosis;

c. in the absence of asbestosis it would be necessary to search the mineral fibers in the biological material, or directly into the lung parenchyma or in the lavage bronchioloalveolar liquid, or with optical microscopy could help as well as scanning or transmission electron microscope;

d. it is therefore known that differential diagnosis of lung adenocarcinoma is not obvious and simple at all.

The markers mentioned in the medical record were negative and it was not specified what markers they were, the cytological and / or histological examination are not reported out and confirmed by immunohistochemical investigation as it should be done. Nothing confirms that the disease was a primary poorly differentiated lung adenocarcinoma and not a different type of lung cancer or a metastasis of a tumor originated elsewhere and first identified in the lung before being evident in other organs (see hypotheses of liver metastatic repetitions).

2. Carcinogenicity of asbestos: although asbestos carcinogenicity is unquestionable, it is also true that the knowledge, work hygiene or compensation legislations, as well as the international scientific databases became acknowledged in the years following those in which Mr. P worked (1955-1992) and commonly accepted in Italy years later. Legislation has in fact evolved thanks to the gradual diffusion of scientific knowledge.

3. Presence of asbestos in the workplace: Mr. P. worked continuously from 1955 to 1992at the maintenance and repair of various types of rail vehicles, first as a workman (Class II, Class I, selected Class I ...) and then as foreman.

There are no data that allow to determine whether and to what extent the patient was exposed to asbestos environmental pollution. The environmental surveys showed the presence of asbestos fibers in very low concentrations, between 0.01 and 0.12 fibers/cc. These measurements were made, however, in areas different from those where the employee worked. It is also missing the official documentation stating the time spent in various environments where asbestos could be present, or the effective exposure of the worker (as already said, in fact, there are only generic and conflicting testimonies; environmental surveys were carried out on workplaces different from those in exam, and showed levels well below TLV and STEL).

Table 2. *TLV-TWA levels*

TLV-TWA	175 f\cc	1948-1967 ACGIH
TLV-TWA	12 f\cc	1968-71 ACGIH
TLV-TWA	5 f\cc	1972-79 ACGIH
TLV-TWA	2 f\cc for chrysotile. 0.5	1980-83 ACGIH
	f\cc for amosite. 0.2 f\cc for crocidolite. 2 f\cc for other	
TLV-TWA Limit value for exposure to chrysotile (daily average)		Legislative Decree no. 277/91, Art. 31, paragraph 1, letter A
TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)		Legislative Decree no. 277/91, Art. 31, paragraph 1, letter B
TLV-TWA	0.1 f/cc	DLgs 81/08 smi
TLV-TWA	0.1 f/cc	ACGIH

4. Chronological criterion: it is known that the latency period of adenocarcinoma is not univocal and it's impossibile to predict it in a single individual because of the influence of different confounding factors (20);

5. Qualitative and quantitative criteria on causation: we note that the criteria which allow to attribute to asbestos the hypothetical lung adenocarcinoma found in the de cuius are completely missing.

a- The radiological investigations carried out provide results in which any indicator of suspected asbestos-related disease (pulmonary fibrosis which is an early sign of pneumoconiosis, asbestosis, pleural plaques, rounded atelectasis)is not mentioned.

b- Lung function exams show an obstructive picture (typical of smoking and not of dust related diseases) no sign of restriction typical of exposure to asbestos.

c- Lung malignancies due to causes other than asbestos (smoke, etc.) do not histologically differ from an asbestos-related cancer, so the existence of a cause-and-effect relationship is to be supposed following criteria scientifically valid.

The difficulty of etiological attribution of lung cancer to asbestos is responsible for heated medical - legal debates, while for pleural mesothelioma the causal role of asbestos is admitted in extremely low doses (21), as regards the cause - effect relationship between asbestos exposure and lung cancer, it is generally believed a cumulative exposure function, with an estimated increase in the risk of 1% for each fiber / ml-years of exposure (22).

To talk about certain etiology biological indicators of past exposure are required (asbestos corpuscles and fibers) the presence of which, besides indicating occurred exposure, allows to quantify the exposure itself and to estimate the risk of neoplastic disease, especially in absence of a concomitant asbestos related pathology as asbestosis. From these premises it is easily deduced that the use of semi-invasive methods, such as bronchoscopy with collection of liquid coming from broncho - alveolar washing, or really invasive methods as transbronchial biopsy procedures would allow to better define the actual load of fibers; these procedures are often necessary if there is a suspicion of an asbestos-related neoplastic disease (23).

According to the Helsinki Consensus Conference in 1997 (24) strict criteria must be met to talk about asbestos related lung cancer, even when it is established that we are dealing with a primary lung cancer. Here are these criteria: simultaneous presence of asbestosis radiologically (absent in this case) or histologically diagnosed, positivity of indicators related to the counting of asbestos corpuscles and fibers: 15,000 asbestos corpuscles (AC) per gram of dry pulmonary tissue, 2 million or more of amphibolic asbestos fibers per gram of dry pulmonary tissue (counting fibers of length> = 5 uM or 5 million counting shorter fibers), or counting corpuscles or fibers in a range compatible with that of asbestosis, or a higher concentration of particles > 1/ml of bronchoalveolar lavage fluid and other. In this particular case these criteria are not met and the presence of these indicators is not even reported nor is the exposure quantified in some way, therefore it is impossible to talk about asbestos-related disease diagnosis and it is impossible to claim which the qualitative-quantitative causation criterion is.

In conclusion, signs of asbestos-related lung disease (interstitial fibrosis, asbestosis, atelectasis, etc.) are absent, and personal or pollution specific measures that allow to quantify a subject's actual exposure to asbestos are absent, and there is no use of indicators of cumulative dose (none of this exists in the documentation). These signs consist of asbestos corpuscles and / or of bare fibers; the search for these indicators must be made in the bronchoalveolar lavage fluid with the most convenient methods, in particular with electron microscopy for fibers mineralogical examination, that allows to have an idea of past exposure. If histological preparations are available, a better characterization of cumulative asbestos exposure seems to derive from the use of the above indicators in combination with the search for asbestos-induced fibrotic lesions (23). They should also be mentioned in the histological examination report.

This to be noted that even if asbestos can be correlated with adenocarcinoma, cigarette smoking alone without any effect attributable to asbestos, may have caused the cancer as an efficient and decisive cause, and many authors in literature associate cigarette smoking with the onset of adenocarcinoma (25, 26, 27, 28, 29, 30, 31).

The concentration is not absolutely suitable in that far below the current law TLV and therefore it is erroneous talking about continuous exposure to high doses of asbestos for over 35 years.

6. Modal criterion on causality: if modal criterion had been met, we should have also found asbestos fibers, asbestos corpuscles, pleural plaques, pulmonary fibrosis or full-blown asbestosis.

7. Criterion for the exclusion of other causes: it is true that the action of smoking is synergistic to that of asbestos but in this case there is no reasonable likelihood of damage resulting from asbestos exposure since there is no clinical or laboratory or radiological sign of asbestos exposure. It 's highly unlikely that this particular lung cancer might be caused by a dose below the TLV fixed by the legislator, who believes that below this value there is not a legitimate chance of developing cancer.

As already mentioned we underline that cigarette smoking alone without any effect attributable to asbestos may have caused the tumor as an efficient and decisive cause, so we can rule out that the disease diagnosed as lung cancer may be connected to asbestos exposure.

Conclusions

There is no certainty of the diagnosis of the lung primitive adenocarcinoma attributed to Mr. P because the diagnostic criteria suggested by the international literature have not been strictly applied.

There are no clinical or instrumental or laboratory signs that can be considered as indicators of effect of asbestosexposure: pulmonary fibrosis, asbestosis, pleural plaques, asbestos fibers, asbestos corpuscles;

The hypotesis of a possible cause and effect relationship is not supported by valid data.

The etiological diagnosis must be in fact supported by tests such as the specific immunohistochemical tests.

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