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LETTERE IN REDAZIONE

Interstitial lung disease in female worker sensitized to epoxy resins: a case report submitted for discussion

Epoxy resins are well known agents in respiratory medicine for their potential to induce bronchial asthma; the possibility of these agents causing respiratory diseases such as asthma, bronchitis, bronchiolitis obliterans with organizing pneumonia (BOOP) and similar lung diseases, has been poorly investigated.

Many years ago, two colleagues and I examined two industrial painters who developed acute pneumonia rapidly evolving in pulmonary fibrosis, after applying marine paints in strictly restricted settings: one (born in 1947, current smoker) from February to April 1994 working in Genoa (Italy) inside the metal columns of an oil rig; the other (born in 1942, who had never smoked) near the end of January 1995 had worked for three days in Ravenna (Italy) inside the shafts of a supply vessel for oil rigs; both had also been previously exposed to asbestos, too. The first patient definitely applied epoxy paints; the second one with all probability applied epoxy paints, although he was not personally aware of the exact nature of the products he used.

The first patient, during the above mentioned job in Genoa, began to suffer from cough, catarrh and emophtoe; chest CT showed enlargement of the mediastinum and local lymph nodes. Extended carnification of the left lung was seen at mediastinoscopy, looking like a neoplasm, and the patient subsequently underwent surgery. His left lung was removed, revealing bronchiolitis, alveolitis, chronic interstitial fibrosis in presence of typical asbestos bodies and fusion of the pleural layers.

The second patient began to cough slightly at the beginning of January 1995, while he shovelled solid and muddy wastes inside the hold of the same supply vessel where afterwards he painted the shafts. He suffered from diffused skin itching, increasing hacking cough, respiratory distress, slight fever, asthenia. During the following two months, itching and fever disappeared while the respiratory distress persisted. In April 1995 a chest CT showed multiple "ground glass" aspects in both lungs. In November 1995 a further chest TC showed just one persisting opacity in the right lung while dyspnoea and asthenia persisted.

A short paper about these two cases was published in an Italian scientific journal, not indexed for PubMed (1).

Recently I examined a case of interstitial lung disease in a woman (born in 1952, who between 1998 and 2002 had smoked 3-4 cigarettes a day). Between October 2004 and April 2006 she had worked in a small factory in Recanati (Italy), where photo frames and other gift articles were produced. These items were made of embossed metallic sheets, externally silvered and internally supported by an epoxy filler. During the last months at this job she suffered from diffused itching, blistering dermatitis, hacking cough, whistling and wheezing; she was recognised as highly sensitized to epoxy resins (patch test) and as a consequence abandoned the factory.

At the factory the woman i) manually poured a fluid epoxy compound to fill up the hollowed metallic sheets; ii) buffed the external silvered side of the items with a solid polishing paste applied with a revolving brush; iii) punched a hallmark on each item.

In May 2006 the Unit for Occupational Safety and Health of which I am responsible ascertained that:

• the filling epoxy compound contained A and F bisphenols (25-30%) and a hardener consisting of 3,6-diazo ctane-1,8-diamine (50-55%), 2,4,6-tri(dimethyl-aminome thyl)phenol (30-36%), benzyl alcohol (4-7%), 3-aminomethyl-3,5,5-trimethyl-cyclohexylamine (1-3%), nonylphenol (1-3%);

• the polishing paste consisted of fatty acids, vegetal and synthetic waxes and "various abrasives" (reasonably amorphous silica and corundum; but not free crystal silica, as the Safety Data Sheet specified);

• the brushing machines were served by local aspirators, but the benches where the fluid epoxy compound was poured were not.

In May 2007 we ascertained that local aspirators had also been installed on these benches.

After the woman abandoned her job in the factory, the dermatitis rapidly disappeared but the respiratory complaints persisted and progressively worsened.

In 2014 a CT revealed diffuse "ground glass" aspects at the bases of the lungs and enlargement of multiple thoracic nodes, while a biopsy showed "sarcomatoid" granulomas in the liver; the whole picture was classified as systemic sarcoidosis. Nothing in the personal history of the patient gave any clues for known extra-occupational risk factors for interstitial lung disease.

It is well known that exposure to epoxy compounds can affect not only skin, but respiratory tissues, too (2), both by sensitization and irritation. The respiratory disease more frequently recognised (mainly in Finland) as caused by epoxy compounds (epoxy resins - bisphenols, epichlorohydrin - and their aminic hardeners, which are strong oxidizers), is bronchial asthma (3-6). Epoxy compounds were reported as capable of inducing bronchitis without asthma (7) and lung disease ("chemical pneumonitis") (8) too. A paper published by Chapman in August 2010 on interstitial lung diseases mentions a syndrome called "epoxy resin lung" attributed to exposure to phthalic anhydride from "heated epoxy resin" (9).

Lung sarcoidosis arises, according to classical concepts, from a mononuclear cell alveolitis evolving into granulomatosis and fibrosis (10). Aetiologies (plural!) of sarcoidosis were reviewed some years ago by Newman LS (11), highlighting that very few studies were conducted about any possible link between sarcoidosis and occupation. Some articles related sarcoidosis with exposure to silica, both in crystalline and amorphous form (12-14). Certainly sarcoidosis consists of a miscellaneous set of similar granulomatous diseases, with different aetiologies and multiple webs of causation.

It seems reasonable to me to propose that the woman's lung disease (like the "chemical pneumonitis" of the two painters), could have been caused or at least triggered by occupational exposures to vapours from epoxy resins and/or their hardeners. Dust exposure, too, (amorphous silica for the woman, asbestos for the painters) could have played a role in the induction of altered immune responses causing inflammation and subsequent lung fibrosis.

Could some cases of "idiopathic" interstitial lung disease, whether falling under the definition of sarcoidosis or not, derive from a BOOP and/or similar syndromes induced by epoxy compounds?

Could *e*poxy compounds and selected mineral agents, especially amorphous silica dusts (and asbestos fibres), interact, altering and modulating the inflammatory and immunological responses in the lung, then leading to fibrosis?

I would be glad to stimulate an exchange of opinions, with the aim of contributing to a better knowledge of occupational lung diseases that until now have been insufficiently understood.

Recently Kreiss (15) affirmed: *"Clinicians need a high index of suspicion for constrictive bronchiolitis in young patients with rapidly progressing exertional dyspnea, regardless of spirometric and radiologic findings. Identification of novel causes and exposure-response relations for known causes are needed to provide guidance for protecting workers at risk for this largely irreversible lung disease."*

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Linfoma non Hodgkin ed esposizione all'asbesto

Nella letteratura sono stati descritti parecchi casi nei quali un mesotelioma maligno e un linfoma non Hodgkin erano insorti nel medesimo soggetto (1, 3, 4-6, 8). L'osservazione di tale associazione patologica suscita vari interrogativi, soprattutto per le implicazioni che essa può rivestire sul piano eziopatogenetico di ambedue le neoplasie.

Negli Stati Uniti una cospicua serie di mesoteliomi, comprendente oltre 3.600 casi, è stata recentemente rivista allo scopo di determinare in quanti di tali casi il tumore mesoteliale fosse associato a neoplasie del sistema ematopoietico (8). Nella serie risultarono compresi 45 casi di tumore maligno ematopoietico: 18 casi di linfomi di Hodgkin, 15 casi di linfomi non Hodgkin, 10 casi di leucemia linfocitica cronica e due casi di leucemia mieloide cronica. Per vari di tali casi di duplice tumore erano disponibili dati sulla storia professionale e/o dati sugli indicatori di esposizione all'asbesto, ma per un buon numero di casi non si avevano notizie in merito. Per una parte dei casi analizzati non era quindi possibile la definizione di mesotelioma asbesto-correlato o non asbesto-correlato. Diciannove casi, 16 con linfoma tipo Hodgkin e tre con linfoma non Hodgkin avevano subito un trattamento radioterapico per il loro linfoma.

In una serie di 169 mesoteliomi pleurici esaminati all'autopsia presso l'Ospedale di Monfalcone furono osservati tre casi di linfoma non Hodgkin: in due di tali casi il linfoma era extralinfoghiandolare, essendo situato rispettivamente nell'encefalo e nel fegato (5).

Nel valutare il significato dell'associazione mesotelioma-linfoma va considerato che il mesotelioma può associarsi non solo al linfoma non Hodgkin ma anche a svariate altre lesioni linfoproliferative o a neoplasie non linfoidi del sistema emopoietico (1, 3, 8). Va tenuto conto inoltre di tutti gli studi che hanno esplorato le possibili relazioni tra malattie da asbesto e neoplasie emopoietiche (1, 3).

Presso l'Ospedale di Monfalcone le caratteristiche dell'esposizione all'asbesto sono state studiate in un gruppo di 14 linfomi non Hodgkin insorti in soggetti con storia e segni obiettivi di esposizione all'asbesto, esaminati all'autopsia nel periodo ottobre 1979-luglio 1984 (6). Le malattie linfoproliferative osservate in questo gruppo comprendevano linfoma diffuso a grandi cellule in cinque casi, linfoma diffuso a grandi e piccole cellule in tre casi, linfoma linfoplasmocitico con macroglobulinemia in due casi, leucemia linfatica cronica in due casi, tricoleucemia in un caso, mieloma in un caso. Nei due pazienti con leucemia linfatica cronica coesisteva un mesotelioma pleurico.

In due casi osservati più di recente, un mesotelioma si era sviluppato rispettivamente in un uomo di 73 anni sottoposto qualche anno prima ad orchiectomia per linfoma non Hodgkin del testicolo (4) e in una donna di 77 anni trattata

Tabella 1 - Linfomi non Hodgkin e patologie da asbesto
Table 1 *- Non-Hodgkin lymphomas and asbestos-related diseases*

Caso	Sesso	Età	Professione	Placche pleuriche	Corpi asbesto	Neoplasie maligne	Bibliografia
1	M	73	cantieri navali	+	rari	Linfoma non Hodgkin del testicolo; mesotelioma pleurico	(4)
2	F	77	cotonificio, distilleria	+		Linfoma non Hodgkin dei linfonodi inguinali; mesotelioma pleurico	(3)
3	M	63	cantieri navali	+	64.000/g tessuto secco	Carcinoma polmonare a stroma linfoide; linfoma non Hodgkin	(2)

qualche anno prima per linfoma non Hodgkin dei linfonodi inguinali (3) (tabella 1, casi 1 e 2). In un altro caso il linfoma non Hodgkin insorto in soggetto con significativa esposizione all'asbesto si contrassegnava per la coesistenza con un carcinoma polmonare a stroma linfoide (2) (tabella 1, caso 3).

L'esame complessivo dei dati disponibili mette in evidenza l'alto numero di associazioni tra tumori asbesto-correlati e neoplasie emopoietiche e la relativa frequenza di localizzazioni inusuali del linfoma in sedi extralinfoghiandolari. Queste ultime sono tipicamente legate all'esistenza di stati di insufficienza immunitaria come si realizzano dopo trapianti d'organo o AIDS. D'altra parte vari studi indicano che l'asbesto può indurre alterazioni rilevanti delle difese immunitarie e ciò supporta l'idea di una relazione causale asbesto-linfoma (7, 9-10).

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