Mediastinal lymph node silicotic nodules and occupational exposure to respirable crystalline silica. A controlled study in patients with lung cancer.

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To the Editor,

Mediastinal lymph nodes (MLN) have recently been pointed out to be key targets in interstitial lung diseases especially in association with environmental exposure (1). In the context of well-defined occupational exposures to respirable crystalline silica (RCS), occurrence of silicotic nodules in MLN without parenchymal silicosis has been clearly identified and considered as an early stage in silicosis leading some authors to coin the term lymph- node-only silicosis (2,3). The carcinogenicity of crystalline silica for lung cancer is now well established (4,5), however in some countries as France lung cancer is still considered an occupational cancer only when associated with silicosis (https://www.inrs.fr/publications/bdd/mp/tableau.html?refINRS=RG%2025). We studied the potential value of identifying silicotic nodules in MLN by pathologists in their standard practice for lung cancer staging to evaluate silica exposure. Medical records of 40 patients of the CaProMat study (6), who had surgery for lung cancer with a standard MLN dissection and an occupational interview were retrospectively reviewed. The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB-Inserm, n° 01-036), and the French Data Protection Authority (CNIL n° 90120). All participating subjects provided informed consent before the interview. The patients completed a detailed occupational history (industry, occupation, job tasks, and duration) through face-to-face interviews, using a standardized occupational health questionnaire (6,7). Thereafter, each questionnaire was analyzed by qualified hygienists to evaluate the probability and intensity of RCS exposure according to each detailed task of the job history. Estimation was made on the basis of the MATGENE silica Job-Exposure Matrix (JEM) related to crystalline silica (8) and literature review. For each job held by subjects, the JEM automatically assigned three semi-quantitative exposure parameters: the probability, frequency and intensity of exposure each with a score from 1 to 3 (7). In summary the dates of beginning and ending of exposure and the respective DIPF (Duration x Intensity x Probability X Frequency) derived score were obtained for each job period. Finally, for each subject the crude total duration of exposure and the summation of the DIPF scores were obtained.

In keeping with the interviews results, the files from 20 patients with a significant silica occupational exposure and 20 without were selected. All the corresponding slides from non-tumoral lung and MLN dissection were retrieved from the pathology department except for two patients from the exposed group (sections were metastatic or slides not available).

Finally, 20 non-exposed and 18 exposed patients were included. A total of 635-hematoxylin-eosin-stained slides were analyzed. No difference was observed when comparing characteristics of the two groups [age 68.0 ±7.29y vs 63.9 ± 8.13y p = 0.118.; gender M/F 18/2 vs 17/1 p=0.676; tobacco smoke (pack-years) 43.6 ± 15.3 vs 38.0 ± 17.2 p=0.291] and the number of nodes examined per patient (18.4 ±8.53 vs19.9± 11.4, p=0.622). Sections were examined for silicotic nodules by two lung pathologists. The examination was completed by polarized light microscopy for identification of crystalline silica and silicate particles. Silicotic nodules were identified as sharply delineated concentric collagen bundles admixed with dust-laden macrophages or entirely fibrotic, associated with birefringent particles (9). As shown in table 1, silicotic nodules were observed in MLN of 13 patients, in 2/20 from the non-exposed group and 11/18 from the exposed group. For each patient non-tumoral tissue was sampled in the resected lung (from upper lobes in 68% of patients, lower lobes in 32%). In three patients intra-parenchymal silicotic nodules were observed. Whatever the group, none of these patients was suspected of pneumoconiosis before surgery. Retrospectively, 15/18 HCRT from the exposed group were reviewed by an expert radiologist, few atypical micronodules were observed in 1/15 (this patient had no silicotic nodules in MLN or lung samples).

A correlation was observed (rho=0.71; p<0.001; Spearman' s correlation test) between the number of nodes in which silicotic nodules were detected and total duration of RCS exposure especially evident after more than 25-30 years of exposure. The curve of the fitted non-linear regression model is shown in figure 1. DIPF score did not add to the cumulative silica exposure parameter for correlation with the presence of silicotic nodules (not shown). While investigating a limited number but well characterized patients using a stringent questionnaire relative to RCS occupational exposure, this study clearly shows the association between the level of exposure and the presence of silicotic nodules in MLN. Conversely their absence does not rule out the occurrence of silica exposure or undetected silicosis. In two patients of the non-exposed group silicotic nodules were observed. An additional interview revealed quasi-professional building hobbies in one patient while no extraprofessional source of exposure was found in the second.

It has long been known that inhaled particles are concentrated in MLN through lymphatic clearance before abnormal accumulation in the lung parenchyma (2,3,10). Parenchymal silicotic nodules were only observed in three patients, a sampling bias could be hypothesized as silicosis is an upper lobe disease, however lung specimens were mainly collected from resected upper lobes. The present study emphasized a dose-response relationship between detection of silicotic nodules in MLN , and RCS exposure , especially evident when the total cumulative duration is above 25-30 years. As reported in the seminal study of Liu et al, a

positive exposure response association between silica exposure and lung cancer was shown with a strongest gradient in risk for 25-year silica exposure (5). Therefore, these results suggest that detection of silicotic nodules in MLN is a marker of significant crystalline silica exposure likely to be associated with an elevated lung cancer risk. They imply that pulmonary pathologists should routinely examine lymph nodes obtained from lung cancer surgery for the presence of silicotic nodules and include these specific evaluations in their routine reporting protocols. Consequently, such identification should 1/ prompt a consultation by an occupational health expert to collect a full exposure history in search of silica exposure, and 2/ recognize that significant exposure to respirable crystalline silica is a potential contributor to the development of the lung cancer which should therefore be evaluated as an occupational disease and considered for compensation purposes even in absence of pulmonary silicosis.

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Table 1: Occupational exposure to respirable crystalline silica and silicotic nodules (SN) identification in mediastinal lymph nodes (LN) from 20 non-exposed (A1: SN negative , A2: SN+) and 18 exposed patients (B) with construction and building trade jobs (B1: SN+ and lung +; B2:SN+ ; B3: SN negative) or others (B4)

Groups	Patients N (Gender M/F)	Age [tobacco pack-years]	Cursus laboris			Silicotic nodules
			Jobs with respiratory crystalline silica occupational exposure	Cumulative duration (years)	DIPF score*	LN+/LN TOTAL **
A1	16 M/2F	57-79 [14-80] [a]	0	0	0	0/ [5-25; 11 ± 5] [b]
A2	2 M [c]	62-73 (50;63]	0	0	0	2/12 1/23
B1	3 M	62-67 [50-80]	Construction and building trades (masons; builder's laborer)	38 44 42	774 699 756	6/21 +lung 6/10 + lung 7/8 +lung
B2	5 M	59-70 [0-51]		45 40 29 38 39	708 720 510 510 564	3/21 9/29 4/8 3/4 6/11
B3	5 M	40-77 [25-50]		31 21 7 26 17	558 252 84 702 105	0/13 0/3 0/23 0/7 0/11
B4	4 M/1 F	57-72 [32-40]	Others (farm-workers; ceramics production; welders)	31 46 43 18 4	366 740 996 36 72	1/18 1/7 4/17 0/12 0/6

- Summation of DIPF (Duration x Intensity x Probability X Frequency) individual job scores

** Nodes with silicotic nodules / total analyzed nodes ; + lung: presence of silicotic nodules in the lung parenchyma

[a] in brackets: range of tobacco consumption

[b] number of MLN analyzed: range; mean ± standard deviation

[c] no occupational exposure recorded; recreative exposure retrospectively found in one patient

Figure legend

Figure 1. Curve of the fitted non-linear regression model (exponential growth equation) (GraphPad Prism) between the number of nodes observed with silicotic nodules and the cumulative duration of respirable crystalline silica exposure expressed in years units.