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

4

5 To the Editor,

6 Mediastinal lymph nodes (MLN) have recently been pointed out to be key targets in
7 interstitial lung diseases especially in association with environmental exposure (1). In the
8 context of well-defined occupational exposures to respirable crystalline silica (RCS),
9 occurrence of silicotic nodules in MLN without parenchymal silicosis has been clearly
10 identified and considered as an early stage in silicosis leading some authors to coin the term
11 lymph- node-only silicosis (2,3). The carcinogenicity of crystalline silica for lung cancer is
12 now well established (4,5), however in some countries as France lung cancer is still
13 considered an occupational cancer only when associated with silicosis (
14 <https://www.inrs.fr/publications/bdd/mp/tableau.html?refINRS=RG%2025>). We studied the
15 potential value of identifying silicotic nodules in MLN by pathologists in their standard
16 practice for lung cancer staging to evaluate silica exposure. Medical records of 40 patients of
17 the CaProMat study (6), who had surgery for lung cancer with a standard MLN dissection
18 and an occupational interview were retrospectively reviewed. The study was approved by the
19 Institutional Review Board of the French National Institute of Health and Medical Research
20 (IRB-Inserm, n° 01-036), and the French Data Protection Authority (CNIL n° 90120). All
21 participating subjects provided informed consent before the interview. The patients
22 completed a detailed occupational history (industry, occupation, job tasks, and duration)
23 through face-to-face interviews, using a standardized occupational health questionnaire
24 (6,7). Thereafter, each questionnaire was analyzed by qualified hygienists to evaluate the
25 probability and intensity of RCS exposure according to each detailed task of the job history.
26 Estimation was made on the basis of the MATGENE silica Job-Exposure Matrix (JEM)
27 related to crystalline silica (8) and literature review. For each job held by subjects, the JEM
28 automatically assigned three semi-quantitative exposure parameters: the probability,
29 frequency and intensity of exposure each with a score from 1 to 3 (7). In summary the dates
30 of beginning and ending of exposure and the respective DIPF (Duration x Intensity x
31 Probability X Frequency) derived score were obtained for each job period. Finally, for each
32 subject the crude total duration of exposure and the summation of the DIPF scores were
33 obtained.

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

38 Finally, 20 non-exposed and 18 exposed patients were included. A total of 635-hematoxylin-
39 eosin-stained slides were analyzed. No difference was observed when comparing
40 characteristics of the two groups [age $68.0 \pm 7.29y$ vs $63.9 \pm 8.13y$ $p = 0.118$.; gender M/F
41 $18/2$ vs $17/1$ $p=0.676$; tobacco smoke (pack-years) 43.6 ± 15.3 vs 38.0 ± 17.2 $p=0.291$] and
42 the number of nodes examined per patient (18.4 ± 8.53 vs 19.9 ± 11.4 , $p=0.622$). Sections
43 were examined for silicotic nodules by two lung pathologists. The examination was
44 completed by polarized light microscopy for identification of crystalline silica and silicate
45 particles. Silicotic nodules were identified as sharply delineated concentric collagen bundles
46 admixed with dust-laden macrophages or entirely fibrotic, associated with birefringent
47 particles (9). As shown in table 1, silicotic nodules were observed in MLN of 13 patients, in
48 2/20 from the non-exposed group and 11/18 from the exposed group. For each patient non-
49 tumoral tissue was sampled in the resected lung (from upper lobes in 68% of patients, lower
50 lobes in 32%). In three patients intra-parenchymal silicotic nodules were observed. Whatever
51 the group, none of these patients was suspected of pneumoconiosis before surgery.
52 Retrospectively, 15/18 HCRT from the exposed group were reviewed by an expert
53 radiologist, few atypical micronodules were observed in 1/15 (this patient had no silicotic
54 nodules in MLN or lung samples).

55

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

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

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

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88

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

165

166

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	774	6/21 +lung 6/10 + lung 7/8 +lung
B2	5 M	59-70 [0-51]		44	699	
				42	756	
				45	708	3/21
				40	720	9/29
B3	5 M	40-77 [25-50]		29	510	4/8
				38	510	3/4
			39	564	6/11	
			31	558	0/13	
			21	252	0/3	
B4	4 M/1 F	57-72 [32-40]	7	84	0/23	
			26	702	0/7	
			17	105	0/11	
			31	366	1/18	
			46	740	1/7	
			43	996	4/17	
			18	36	0/12	
			4	72	0/6	

167

168 • Summation of DIPF (Duration x Intensity x Probability X Frequency) individual job scores
 169 ** Nodes with silicotic nodules / total analyzed nodes ; + lung: presence of silicotic nodules in
 170 the lung parenchyma

171 ^a in brackets: range of tobacco consumption

172 ^b number of MLN analyzed: range; mean ± standard deviation

173 ^c no occupational exposure recorded; recreative exposure retrospectively found in one patient

174

175

176 Figure legend

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