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Clinicopathological Study of 50 Cases of Lung Cancer Associated with Silicosis*

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ABSTRACT : To clarify any causal relationship between lung cancer and silicosis, we studied clinicopathological findings in 50 men, mainly tunneling workers, aged from 47 to 85 years with both diseases. The histological types were : squamous cell carcinoma, 29 cases; small cell carcinoma, 10; adenocarcinoma, 6; large cell carcinoma, 4; and adenosquamous carcinoma, 1. The high frequency of cancer, particularly squamous and small cell cancer, in sites of silicotic fibrosis suggested a causal relationship, perhaps via a carcinogen. If a weak carcinogen accumulastes in fibrotic leasions, its prolonged presence may induce cancer. We believe that silica alone is rarely carcinogenic, but it may interact with polycyclin aromatic hydrocarbons from cigarette smoking or from pyrolysis, or with other substances encountered in occupational environments.

INTRODUCTION

Pneumoconiosis is defined as the accumulation of dust in the lung, and the tissue reactions to its presence. It is an occupational lung disorder mainly involving fibrosis of the lungs due to dust. There are a large number of inorganic dusts that give rise to pneumoconiosis, the most common of which is silicon dioxide (SiO_2) inducing silicosis. These dusts include chrome dust, nickel dust, beryllium dust and asbestos dust, all of which are known to possess carcinogenic action as well as causing fibrosis, but SiO_2 is generally considered not to cause cancer. Recently, however, many studies suggesting a correlation between silicosis and lung cancer have been published. We have carried out clinical and pathological examinations of 50 cases of silicosis associated with lung cancer, and herein discuss the mode of development of lung cancer in such cases.

MATERIALS AND METHODS

The subjects of this study were 50 patients with lung cancer accompanying silicosis, diagnosed between January 1975 and February 1988. All were men, and their ages at the time of diagnosis ranged from 47 to 85, with a mean of 63.5 ± 8.8 years. During a period of an observation extending until August 1988, 28 of the 50 patients died. The duration of exposure to dust varied from 3 years to 42 years, with a mean of 15.1 ± 8.6 years. These subjects had contracted silicosis as a result of tunnel construction, roadbuilding, or dam construction; and in all of them, chest radiographs were marked with small or large opacities. Forty-eight of them (96.0%) were smokers, and 44 (88.0%) were smoking heavily, with smoking indeces (number of cigarettes smoked per day × number of years of smoking) of 400 or more.

In each case, we recorded the site of the

accompanying lung cancer, its tissue type according to the WHO histopathological classification, and its stage based on the TNM classification, and analyzed the characteristics of lung cancer accompanying silicosis. We also followed up each case to observe its course and outcome.

RESULTS

The locations of development of lung cancer were as follows: the upper lobe of the left lung, 17 cases; the lower lobe of the right lung, 15 cases; the upper lobe of the right lung, 9 cases; the lower lobe of the left lung, 5 cases; the middle lobe of the right lung, 4 cases (Table 1).

Table 1. Location of Lung Cancer

Location		Hilar	Peripheral	Total	(%)
Left	Upper lobe	7	10	17	(34.0)
	Lower lobe	0	5	5	(10.0)
Right	Upper lobe	4	5	9	(18.0)
	Middle lobe	1	3	4	(8.0)
	Lower lobe	1	14	15	(30.0)
	Total	13	37	50	(100%)

Thus, there were 28 cases in the right lung and 22 in the left; the upper and middle lobes accounted for 30, and the lower lobe for 20. Moreover, the lower lobe sites tended to occur more often in the superior segment (S^6): right lung S^6, 7 cases; and left lung S^6, 3 cases. We classified the lung cancer as hilar type when it occurred from the segmental bronchi to the large, central bronchi, and as peripheral type in sites from the subsegmetal bronchi to the small, peripheral bronchi. There were 37 cases of the peripheral type and 13 of the hilar type.

The number of cases of each tissue type, on the basis of the WHO histopatholgical classification, was as follows: 29 of squamous cell carcinoma (58.0%), the most common; 10 of small cell carcinoma (20.0%); 6 of adenocaricinoma (12.0%); 4 of large cell carcinoma (8.0%); and 1 of adenosquamous carcinoma (2.0%) (Table 2). The frequencies of squamous cell carcinoma and small cell carcinoma were higher than in the general male population of Japan, and that of adenocarcinoma was lower.

Table 2. Histological Type of Lung Cancer

Histological Type	Hilar	Peripheral	Total	(%)
Squamous cell carcinoma	9	20	29	(58.0)
Small cell carcinoma	3	7	10	(20.0)
Adenocarcinoma	0	6	6	(12.0)
Large cell carcinoma	1	3	4	(8.0)
Adenosquamous carcinoma	0	1	1	(2.0)
Total	13	37	50	(100%)

Table 3. Stage of Lung Cancer

Histological Type	I	II	III	IV
Squamous cell carcinoma	15	3	7	4
Small cell carcinoma	1	0	3	6
Adenocarcinoma	1	1	0	4
Large cell carcinoma	0	0	1	3
Adenosquamous carcinoma	0	0	0	1
Total	17	4	11	18
(%)	(34.0)	(8.0)	(22.0)	(36.0)

The peripheral type was common in every histological category, including squamous cell carcinoma and small cell carcinoma.

As for the staging of the cancers seen, based on the TNM classification, there were 17 cases (34.0%) at stage I, 4 cases (8.0%) at stage II, 11 cases (22.0%) at stage III, and 18 cases (36.0%) at stage IV (Table 3). We removed the tumors surgically in 22 of the 50 cases (44.0%). Histopathological examination revealed five cases of early-stage hilar lung cancer in which the neoplasms were confined to the walls of the large bronchi and no metastases were seen either in the lymph nodes or at distant locations; and there were two cases of early-stage peripheral lung cancer-tumors of the peripheral type with diameters of 2cm or less, and without either lymph node or distant metastases (Table 4).

Of the 22 cases treated by surgical resection up to August 1988, six (27.3%) have died. The survival times of these patients were from eight months to two years eleven months, with a mean of one year eight months. The cause of death was recurrent lung cancer in three cases, concomitant stomach cancer in two, and concomitant renal cancer in one. Sixteen cases (72.7%) remained alive after observation periods extending from six months to 11 years, seven of these cases surviving for three of more years postoperatively, and one for 11 years. We

Table 4. Patients with Early-Stage Lung Cancer

Case	Age Sex	Smoking index*	Histology	Location	Size (mm)	Depth of invasion
1	72, M	1040	Squamous	r-UB†	15×12	Submucosal
2	68, M	800	Squamous	l-UB	5×5	Submucosal
3	50, M	375	Squamous	r-UB	14×11	Cartilaginous
4	54, M	600	Squamous	r-B^2	3×3	Cartilaginous
5	59, M	520	Squamous	l-UB	5×6	Intramucosal
6	74, M	340	Squamous	l-S^3	17×13	
7	67, M	900	Squamous	l-S^6	14×13	

* Number of cigarettes smoked per day × number of years of smoking
† Right upper lobe bronchus

detected no signs of recurrence in these cases, and expect them to survive even longer.

In 28 cases we did not attempt surgical intervention, either because the lung cancer was at an advanced stage, or because of the impairment of respiratory function; and 22 of these patients (78.6%) have already died. The survival times of those who have died vary from one month to four years nine months, with a mean of ten months; but most died within one year of lung cancer being diagnosed. The patients who were not operated on included one with concurrent skin cancer, and one with concurrent thyroid gland cancer, but the direct cause of death in each case was the lung cancer.

Concomitant cases of cancer seen in other organs totalled five out of 50 cases (10.0%). The organs concerned were the stomach (in two cases), and the kidney, skin and thyroid gland (in one case each). The two stomach cancer cases were heterochronic cases, discovered over a year after we performed operations for lung cancer, whereas the renal and skin cancer cases were synchronic. The thyroid cancer was latent, and we found it only on post-mortem examination.

DISCUSSION

Many researchers have reported on the relationship between pneumoconiosis and lung cancer since Rostoski *et al.*[1] published 'Schneeberger Lungenkrebs' (1926). It is difficult to conduct accurate long-term follow-up studies among foundry workers, since many of them quit their jobs and move to new ones, with the result that there are both studies which recognize a cause-and-effect relationship between these two diseases[2~4] and those that do not[5~7], and no concurrence of opinion has yet been reached.

Westerholm[2] carried out a cohort study of mining, quarrying and tunneling occupations, which appeared in the Swedish Pneumoconiosis Register. He reported that the lung cancer proportionate mortality rate (PMR) among silicosis patients diagnosed between 1931 and 1948 was 590 ($p<0.01$), and for those diagnosed between 1949 and 1969, the PMR was 380 ($p<0.01$). These rates were significantly higher than the Swedish national lung cancer rates, as was the PMR of 220 for the steel and iron industries between 1949 and 1969.

Finkelstin *et al.*[3] investigated the mortality of 1190 Ontario miners who had received Workman's Compensation for silicosis between the years 1940 and 1975, and compared the results with the mortality of the general male population of Ontario. They reported that the lung cancer mortality rate among miners first receiving compensation from 1940 through 1949 was three times as high as among the general population (PMR=303), and that in miners initially compensated from 1950 through 1959 was twice as high (PMR=195), while among those compensated since 1960 mortality rates have been similar to those of Ontario males in general.

Gudbergsson *et al.*[4] conducted a cohort study of 331 male silicosis patients registered in the Finland Register of Occupational Diseases between the years 1964 and 1974, and found that the observed/expected ratio for lung cancer in the silicosis cohort was 3.0 ($p<0.01$)-significantly

higher than in the general male population.

In Japan, since Takeda *et al.*[8] in 1964 published findings to the effect that in ten (20.0%) out of 50 autopsies of silicosis cases, the silicosis was accompanied by lung cancer, attention has been directed to the ralationship between these two diseases, and Kikuchi *et al.*[9] had by 1979 detected lung cancer in 64 autopsies of silicosis cases (15.8%) out of 406.

Chiyotani[10] carried out a prospective cohort study between 1979 and 1983 in 11 institutions in Japan, and obtained a high observed/expected ratio of 4.1 for the silicosis cohort.

We have published reports on the high lung cancer rates among patients who had contracted silicosis through tunneling operations in Oita Prefecture, Japan[11)12)13)]. In a group of 50 patients with lung cancer accompanying silicosis whom we examined, we discovered that the ratio of tissue types differed from that of the general Japanses male lung cancer population, squamous cell carcinoma and small cell carcinoma being more common, and adenocarcinoma less common. This suggests some kind of carcinogenic activity on the part of silicosis, but the frequency of squamous cell carcinoma was nor as high as among cases of lung cancer caused by chromium, one of the principal carcinogens in occupational lung cancer. The site of occurrence of the cancer is also significant: although lung cancer resulting from the inhalation of carcinogens more frequently takes place in the hilar bronchi, we saw a higher frequency of sites in the peripheral bronchi. Also, the upper lobe and the superior segments (S^6) of the lower lobe were sites of frequent occurrence, which coincided with the sites of major fibroplastic changes of silicosis. These facts suggested that the carcinogenicity of SiO_2 is non-existent or extremely weak, but we presumed that, since SiO_2 or other simultaneously inhaled carcinogens may remain in closely circumscribed areas for long periods owing to the fibroplastic changes of silicosis, they may show carcinogenic action. Alternatively, the condition known as scar cancer may arise from the fibroplastic changes, but since adenocarcinoma generally accounts for the highest proportion of scar cancers, it is likely that some carcinogenic substance was a contributory factor.

The results of many animal experiments dealing with carcinogenesis as a property of silica have been negative, but when Stenbäck and Rowland[14] instilled SiO_2 alone into the trachea of Syrian golden hamasters, although they saw no tumorigenesis, when benzo(a) pyrene (Bap) was administered simultaneously, the rate of respiratory tract tumor development was higher than with BaP administration alone. Ther therefore reported that, because of its prolongation of the local retention time of BaP, SiO_2 strengthened Bap's carcinogenetic capacity.

Holland *et al.*[15] administered Min-U-Sil, spent shale particulates, and raw shale particulates separately to members of groups of Syrian hamsters, Sprague-Dawley rats, and Fisher-344 rats. In 15% of the Sprague-Dawley rats to which a high dose of Min-U-Sil, 7mg/week, was given intratracheally, and in 27% of the F-344 rats that inhaled an airborne concentration of $12mg/m^3$ of Min-U-Sil for 6 hours per day, 4 days per week, for 24 months, respiratory tumors developed. The results of the experiments of Stenbäck and Rowland indicated that silica contributed no carcinogenesis as a cocarcinogen or a promoter, and those of Holland *et al.* suggested that it may even act as a direct carcinogen.

Foundry workers are reported to smoke cigarerttes more than average male subjects, and to start smoking at an earlier age[10]. Among our 50 subjects with lung cancer accompanying silicosis, only two were non-smokers, so that 48 (96.0%) were smokers. Moreover, 44 (88.0%), smoked heavily, and we believe that the carcinogens contained in the tobacco may well have accumulated in the fibrosed leaions, increasing the carcinogenic effects of smoking. Foundry workers probably inhale minute quantities of carcinogens other than silica (such as radon daughters, asbestos, arsenic; or polycyclic aromatic hydrocarbons as products of organic combustion), and the presence of silica may reinforce the carcinogenic effects of these substances[16].

In addition to small and large opacities, rediographs of the chest in cases of silicosis show the shadows of pneumonia, pulmonary

tuberculosis, bronchitis, emphysematous changes, or pleuritic lesions, each of which makes detection of early lung cancer difficult. When the radiographs of silicosis patients are being interpreted, they must be compared with previous radiographs and examined with meticulous care so that no change, even if very small, is overlooked. Fiberscopic transbronchial lung biopsy and transbronchial lung brushing are extremely useful techniques for the early diagnosis of lung cancer[12].

By means of an aggressive program of fiberscopic examinations of our silicosis, patients, we were able to detect early-stage lung cancer and carry out surgical resection in 22 cases (44.0%) out of 50. The prognoses for those who underwent resection were distinctly more favorable than the prognoses for those who did not. Depression of respiratory function is common in patients with lung cancer associated with silicosis, the lymph nodes show fibrous adhesions to the bronchi and the pulmonary blood vessels, and sutural defects and air leakages are liable to occur because of pleural adhesions and emphysematous and fibrous changes, so that various technical problems are involved in their surgical treatment. However, as long as surgical resection is feasible, a lengthy survival period can be expected, and so, just as in the case of general lung cancer, efforts must be made to detect lung cancer in association with silicosis at the earliest possible stage, and likewise, to carry out early resection.

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