Virchows Archiv A Pathol Anat (1992) 420:463–471

Virchows Archiv A
Pathological Anatomy and Histopathology

Incidence of atypical bronchioloalveolar cell hyperplasia of the lung: relation to histological subtypes of lung cancer

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Received May 1, 1991 / Received after revision September 27, 1991 / Accepted October 1, 1991

Summary. The incidence of atypical bronchioloalveolar cell hyperplasia (ABH) of the lung was investigated to evaluate the possiblity of this lesion being a precancerous stage in the histogenesis of adenocarcinoma. Lobectomy and pneumonectomy specimens of 165 primary and 45 metastatic tumour cases were step-sectioned horizontally and examined histologically. An average of 51 blocks were taken in each case. Sixty-seven ABHs up to 10 mm in diameter were detected, only 2 lesions being associated with scar tissue. Age was one factor apparently related to ABH development, although not the major one. There was no correlation between smoking index and ABH occurrence. In males, the incidence was highest in association with adenocarcinoma (25.5% of cases, 0.8% of sections), followed by large cell carcinoma (25.0% of cases), squamous cell carcinoma (10.5% of cases) and metastatic tumours from other sites (4.8% of cases). In females, ABH was also more common together with adenocarcinoma (8.3% of cases) than with metastatic tumours (4.0% of cases). The differences in male incidences by case and by section between the adenocarcinoma and metastatic tumour categories were statistically significant ($P<0.05$, $P<0.01$ respectively) indicating that ABH may be a precancerous lesion capable of transformation of adenocarcinoma.

Key words: Atypical bronchioloalveolar cell hyperplasia – Lung – Adenocarcinoma – Histogenesis – Precancerous conditions

Introduction

Lung cancer in Japan, which has recently shown a steep increase in incidence, is characterized by a high proportion of adenocarcinoma and relatively low rates for squamous and small cell carcinoma (Tsuchiya et al. 1982; Tanaka et al. 1988; Morita and Sugano 1990) when compared with data for the United States. However, a rising incidence of adenocarcinoma has also been reported in the United States (Valaitis et al. 1981; Percy and Sobin 1983). In squamous cell carcinoma, squamous metaplasia has been studied systematically and a metaplasia-carcinoma sequence has been established (Auerbach et al. 1957; Tsuchiya et al. 1987). However, the histogenesis of adenocarcinoma remains unclear, although some attention has been paid to atypical bronchioloalveolar cell hyperplasia (ABH) as a possible precancerous lesion (Yanagisawa 1959; Meyer and Liebow 1965; Kodama et al. 1986; Miller et al. 1988; Weng et al. 1990). The term refers to atypical focal proliferative lesions comprising cuboidal or columnar cells replacing pre-existing alveolar and/or bronchiolar epithelium. In previous reports, ABH has been variously named, for example, as atypical epithelial proliferation (Meyer and Liebow 1965), glandular neoplasia (Miller et al. 1988) and atypical cuboidal cell hyperplasia (Kodama et al. 1986). Earlier studies related ABH and the development of lung cancer to scar formation or honeycombing in the lung (Raeburn and Spencer 1953; Meyer and Liebow 1965). However, a systematic investigation of ABH has not yet been conducted adequately.

In the present study, attention was concentrated on the relationship of ABH to different histological types of lung cancer as well as its association with lung scars.

In our hospital, lobectomy is the main operative procedure applied to metastatic tumours of non-lung origin (Nakagawa et al. 1978) and this provided the most appropriate control group for comparison with primary cancers.

Materials and methods

Consecutive surgically resected lung specimens in the Cancer Institute Hospital, Tokyo, during 1984–1987 were used for this prospective study. Partial resection specimens and lungs with severe pneumonia were excluded from the study. Also excluded were lungs from patients undergoing pre-operative radiotherapy and chemotherapy. The cases investigated were divided into two groups:

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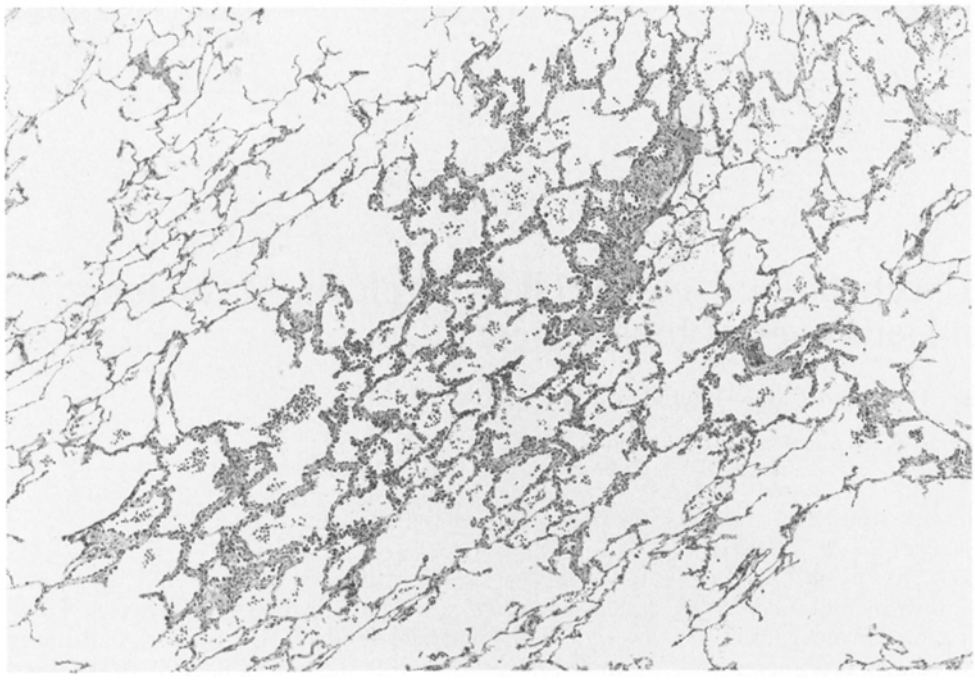

Fig. 1. Low magnification view of atypical bronchioloalveolar cell hyperplasia (ABH) illustrating a focal proliferative epithelial lesion in the periphery of the lung, replacing pre-existing alveolar epithelium and demonstrating a gland-like appearance. H & E, ×55

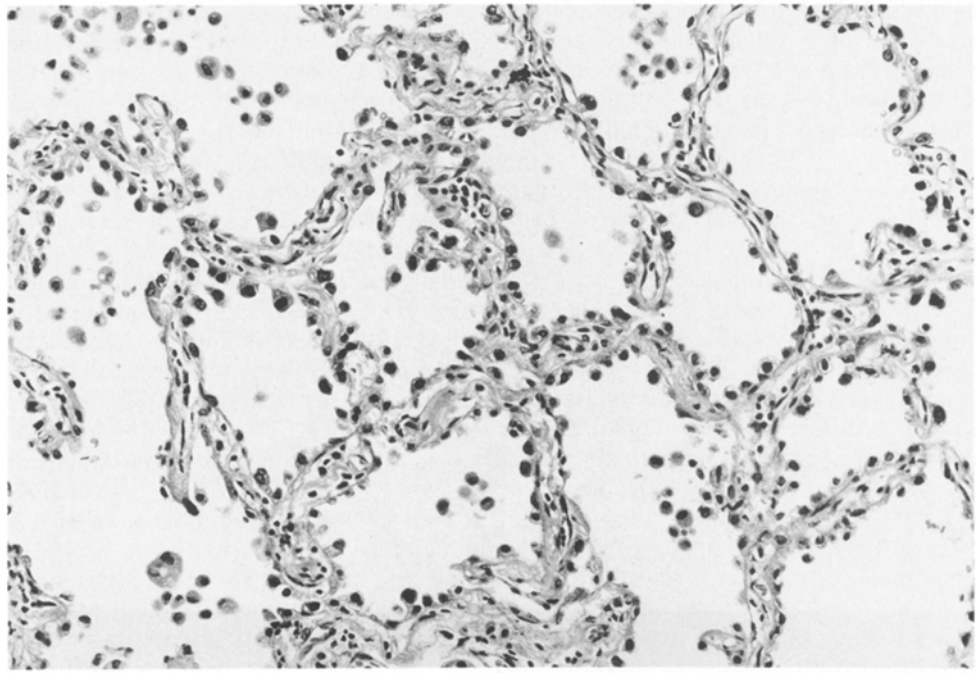

Fig. 2. High magnification view of an ABH (grade I) consisting of cuboidal and oval cells lining slightly to moderately thickened septa. Note variation in size and shape of cells and the hyperchromatic nuclei. H & E, ×220

group A composed of 165 lungs from 110 males (pneumonectomy 12, lobectomy 98) and 55 females (pneumonectomy 4, lobectomy 51) resected for primary lung cancer; group B comprising 45 lungs from 21 males (lobectomy 21) and 24 females (pneumonectomy 1, lobectomy 23) resected for metastatic carcinoma and sarcoma (36 and 9 cases, respectively) considered to be the control group. Sex and occupation, but not age or smoking history, were matched in both groups. These possible influences on ABH development were also analysed. The resected lungs were perfused with 10% formalin through the bronchial tree and were sliced serially at 5-mm intervals in the horizontal plane. The slices containing the largest diameter of the tumours and all the lung tissues of the apical (S^1) or apicoposterior segments (S^{1+2}) of the upper lobe and the superior segments (S^6) of the lower lobe were cut into standard blocks (2 × 1 cm) because these segments contain frequent sites of adenocarcinoma development in the lung (Honda et al. 1983).

All the tissues were processed according to standard procedures for preparation of haematoxylin and eosin-stained histological sections and examined microscopically. Periodic acid-Schiff and alcian blue staining were added in the examination of adenocarcinomas and poorly differentiated carcinomas. Additionally elastic van Gieson staining was performed to demonstrate fibrosis and elastosis. Sections in which tumour tissue occupied more than 80% of the total area were excluded. The numbers of sections examined varied from case to case, ranging from 11 to 148. The average number

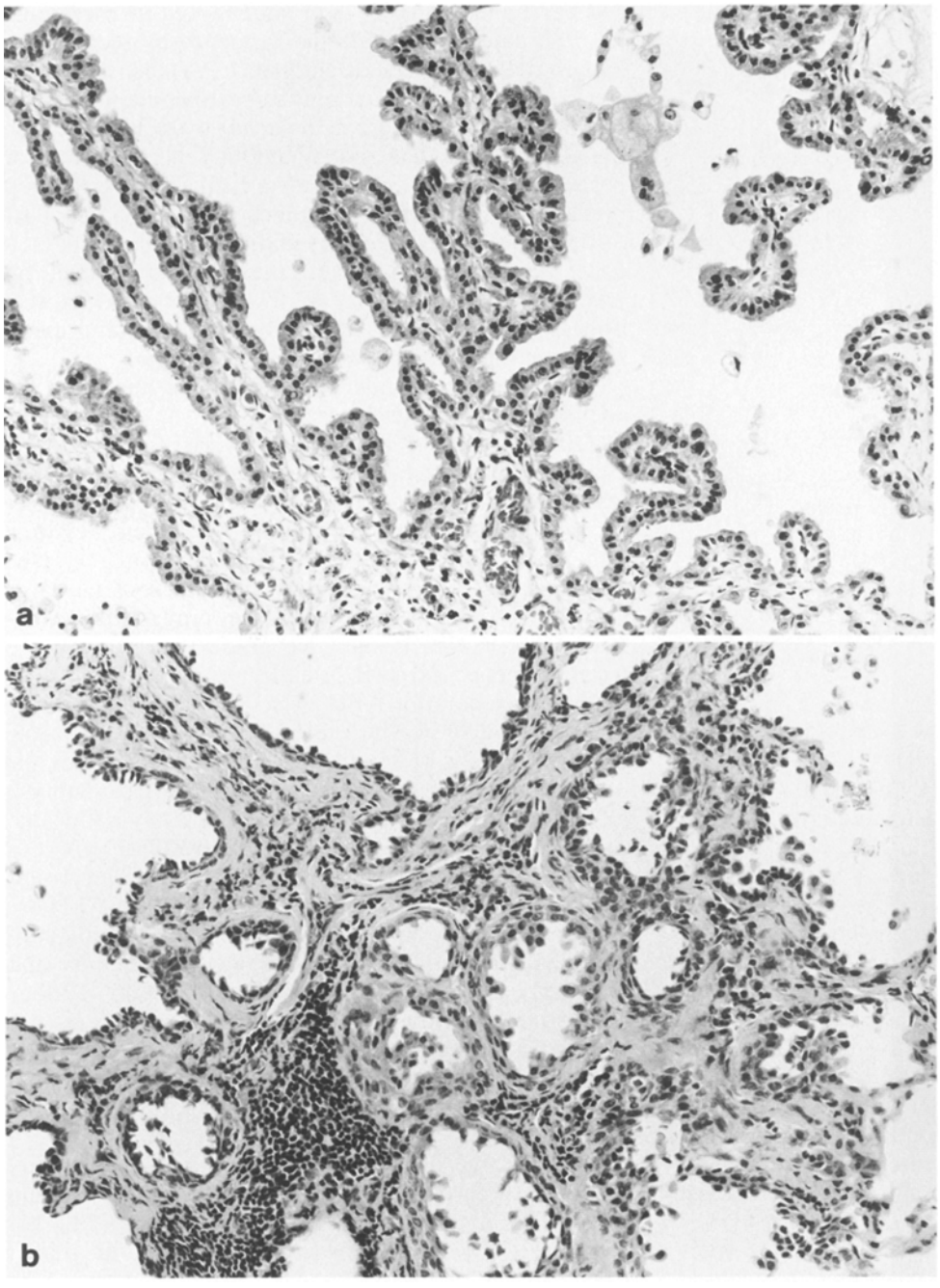

Fig. 3a, b. High magnification view of ABHs (grade II). **a** ABH consisting of columnar and cuboidal cells forming a continuous proliferating epithelium on moderately thickened septa. Variation in size and shape of cells is observed. H & E, ×220. **b** ABH consisting of cuboidal and columnar cells demonstrating partial piling up on moderately thickened septa with acinar formation. H & E, ×220

of sections per case was 55.0±21.2 for males and 44.9±16.3 for females of group A, and 52.8±25.5 for males and 47.1±24.5 for females of group B. The lung cancers were classified according to the WHO classification (WHO 1981). ABH is defined as: a peripheral focal proliferative lesion, short of frank malignancy, consisting of atypical cuboidal and/or columnar epithelial cells with hyperchromatic nuclei and prominent nucleoli, replacing pre-existing alveolar or bronchiolar epithelium and having a glandular appearance. Alveolar septa in most instances are thickened by elastofibrosis, but the alveolar architecture is basically preserved (Figs. 1–3). Lesions which were considered to be possible metastatic foci were eliminated.

ABH was separated into two grades: grade I with mild atypia (Fig. 2), featuring slightly atypical epithelial cells proliferating in single layers intermittently or continuously on septa which are in most instances slightly thickened; and grade II with marked atypia (Fig. 3a, b), featuring atypical epithelial cells proliferating continuously in single or multiple layers on thickened septa, with papillary and/or acinar formation.

Diagnosis of elastosis or fibrosis in ABH lesions was applied to an apparent increase of elastic or collagen fibres in the septa in comparison with the normal alveolar framework in the same specimen. Diagnosis of scarring was applied to elastofibrotic areas occupying more than one-sixth of the microscopic visual field, using X40 magnification, in the peripheral lung tissue.

For statistical analysis, the chi-square test was used.

Results

Sixty-seven examples of ABH were detected in 29 of the 210 cases examined.

Table 1. Size of atypical bronchioloalveolar cell hyperplasia (ABH) lesions

Size (mm)	No. of lesions (%)
$D \leq 1$	17 (25.4)
$1 < D \leq 3$	37 (55.2)
$3 < D \leq 5$	7 (10.4)
$5 < D \leq 10$	6 (9.0)
Total	67 (100.0)

D, Diameter

Table 2. Incidence of ABH by case and by section

Sex	Group	Case		Section	
		No. examined	Incidence (%)	No. examined	Incidence (%)
Male	A	110	20.0	6052	0.7 *
	B	21	4.8	1108	0.1 *
Female	A	55	9.1	2391	0.9
	B	24	4.0	1131	0.4

* $P < 0.01$ (chi-square test)

The lesions varied from less than 1 mm to 10 mm in diameter, most of them being small and not exceeding 5 mm (Table 1).

The incidences of ABH in groups A and B by case (% of positive cases) and by section (% of positive sections) are presented in Table 2. Higher values were found in group A in both sexes, by case and by section, and the difference in the incidence by section between male groups A and B was statistically significant ($P < 0.01$).

The incidence data for ABH relative to the histological subtype of pulmonary carcinoma in group A are shown in Table 3. Although ABH was recognized together with small cell and adenosquamous carcinomas in males and with squamous cell carcinomas in females, the numbers of cases were too small to allow statistical analysis.

In males, the incidence by case was found to be highest in the adenocarcinoma (25.5%) and then in the large cell carcinoma (25.0%) and squamous cell carcinoma (10.5%) categories, while the incidence by section was highest in the large cell carcinoma (1.7%) then adenocarcinoma (0.8%) and squamous cell carcinoma (0.2%) categories. The differences in incidence by section between the adenocarcinomas and squamous cell carcinomas or between large cell carcinomas and squamous cell carcinomas were statistically significant ($P < 0.05$, $P < 0.01$ respectively). A statistically significant difference in incidence was recognized between the adenocarcinomas and metastatic tumours ($P < 0.05$ by case, $P < 0.01$ by section) and between the large cell carcinomas and metastatic tumours ($P < 0.01$ by section) in males.

In females, the incidence of ABH was highest in the adenocarcinoma cases by section.

Out of 67 ABHs, 48 and 19 were classified as a grade I and grade II, respectively (Table 4). Grade II lesions were detected in all male subtypes of primary lung cancer except adenosquamous carcinoma. In females, they were only associated with the adenocarcinoma category. The lesions were seen as multiple entities in 2 of the large cell carcinoma cases in males and in only 1 adenocarcinoma case in the females. No grade II lesion was detected in metastatic cases of either sex.

Incidence data for ABH by section relative to degree of atypia are shown in Table 5. Grade I lesions in the male group A were found in the same order as for the incidence of total ABH relative to histological subtype (Table 3), but the incidence of grade II ABH in the adenocarcinoma category was relatively low (0.2%).

We detected 12 cases with multiple ABH. The groups and the subtypes of lung cancer with multiple ABH are shown in Table 6. In males, multiple ABH were identified in 7.8% and 25.0% of the adenocarcinoma and large cell carcinoma cases, respectively. In females, they were found together with squamous cell carcinomas (20.0%), adenocarcinomas (6.3%) and in 1 group B case (4.2%). The numbers of ABH per individual case was 6 or less except in 1 female case of adenocarcinoma with 14 lesions.

Data on age distribution of the examined cases are summarized in Table 7. Although mean age in group A was higher than that of group B in both sexes, the differences were not statistically significant. In males, the mean age of cases with ABH was higher than that

Table 3. Incidence of ABH by histological type of carcinoma in group A

Sex	Subtype of carcinoma	No. of cases	Incidence (%)	
			By case	By section
Male	Squamous cell ca	38	10.5	0.2 * **
	Small cell ca	4	25.0	0.4 * **
	Adenocarcinoma	51	25.5	0.8 * **
	Large cell ca	12	25.0	1.7 **
	Adenosquamous ca	5	20.0	0.4
Female	Squamous cell ca	5	20.0	0.8
	Small cell ca	1	0	0
	Adenocarcinoma	48	8.3	0.9
	Large cell ca	1	0	0

* $P < 0.05$, ** $P < 0.01$ (chi-square test)

Table 4. Degree of atypia of ABHs relative to tumour histology by case

Sex	Group	No. of lesions		
		Degree of atypia		Total
		Grade I	Grade II	
Male	A	27	14	41
	Squamous cell ca	2	2	4
	Small cell ca	0	1	1
	Adenocarcinoma	17	5	22
	Large cell ca	6	7[a]	13
	Adenosquamous ca	1	0	1
	B	1	0	1
Female	A	16	5	21
	Squamous cell ca	2	0	2
	Small cell ca	0	0	0
	Adenocarcinoma	14	5[b]	19
	Large cell ca	0	0	0
	B	4	0	4
Total		48	19	67

[a] These lesions were as multiple entities in two cases (3 and 4 in each case)
[b] All lesions seen in one case

Table 5. Degree of atypia of ABHs relative to tumour histology by section

Sex	Group	Incidence of ABHs (%)	
		Grade I	Grade II
Male	A	0.4	0.3
	Squamous cell ca	0.1	0.1
	Small cell ca	0 *	0.4 *
	Adenocarcinoma	0.6 *	0.2 *
	Large cell ca	0.8	0.9
	Adenosquamous ca	0.4	0
	B	0.1	0
Female	A	0.7	0.2
	Squamous cell ca	0.8	0
	Small cell ca	0	0
	Adenocarcinoma	0.7	0.2
	Large cell ca	0	0
	B	0.4	0

* $P<0.01$ (chi-square test)

Table 6. Data on multiple ABH cases

Sex	Group	No. of cases examined	No. of multiple ABH cases (%)	No. of cases by No. of ABH lesions					
				2	3	4	5	6	14
Male	A	110	7 (6.4)						
	Adenocarcinoma	51	4 (7.8)	1	2		1		
	Large cell ca	12	3 (25.0)	1			1	1	
	B	21	0 (0)						
Female	A	55	4 (7.3)						
	Squamous cell ca	5	1 (20.0)	1					
	Adenocarcinoma	48	3 (6.3)	2					1
	B	24	1 (4.2)			1			
Total		210	12 (5.7)						

Table 7. Age distribution of cases examined

Sex	Group	Mean age ± SD (No. of cases)		
		ABH+	ABH−	Total
Male	A	66.8 ± 7.7 (22)	65.0 ± 9.9 (88)	65.4 ± 9.5 (110)
	Squamous cell ca	66.0 ± 8.0 (4)	64.6 ± 9.6 (34)	64.9 ± 9.4 (38)
	Adenocarcinoma	68.3 ± 7.9 (13)	64.1 ± 10.8 (38)	65.3 ± 10.2 (51)
	Large cell ca	66.3 ± 1.5 (3)	65.4 ± 9.5 (9)	65.6 ± 7.6 (12)
	B	57 (1)	57.7 ± 10.5 (20)	57.6 ± 10.2 (21)
Female	A	63.4 ± 12.0 (5)	62.5 ± 9.8 (55)	62.5 ± 9.9 (60)
	Adenocarcinoma	60.5 ± 11.6 (4)	62.5 ± 9.7 (44)	62.3 ± 9.8 (48)
	B	40 (1)	59.1 ± 9.6 (23)	58.3 ± 10.2 (24)

Table 8. Smoking index in cases examined

Sex	Group	Mean smoking index[a] ± SD (No. of cases)		
		Multiple ABH	With ABH	Without ABH
Male	A	1103.9 ± 509.8 (7)	818.2 ± 568.0 (22)	1062.8 ± 948.0 (88)
	B	–	0 (1)	502.0 ± 337.5 (20)
Female	A	422.5 ± 494.0 (4)	402.0 ± 430.3 (5)	254.9 ± 573.0 (50)
	B	285.0 (1)	285.0 (1)	8.7 ± 40.5 (23)

[a] Smoking index: no of cigarettes per day × smoking years

Table 9. Data on ABH in slices with the largest diameter of tumour

Case no.	Histology of tumour	No. of ABH lesions	No. of lesions by distance from the tumour (mm)				
			1	3	5	6	10
1	Squamous cell ca	2			1	1	
2	Squamous cell ca	1					1
3	Adenocarcinoma	5	1			1	3
4	Adenocarcinoma	2			1	1	
5	Adenocarcinoma	1					1
6	Large cell ca	3		1			2
7	Large cell ca	1					1
8	Metastatic tumor	1					1
Total		16	1	1	2	3	9

Table 10. Relationship of size of ABH to septal elastofibrosis or scar

Size (mm)	No. of examined lesions	Septum		Scar No. of positive lesions
		No. of positive lesions		
		Elastosis	Fibrosis	
$D \leq 1$	13	10	3	0
$1 < D \leq 3$	17	17	7	1
$3 < D \leq 5$	4	3	2	0
$5 < D \leq 10$	4	4	2	1
Total	38	34	14	2

of cases without ABH in group A and also in the histological subgroups, although again the differences were not statistically significant. In females, the mean age of adenocarcinoma cases with ABH was slightly lower than that of cases without ABH.

Data on smoking for the cases examined are shown in Table 8. In females, the mean smoking index was larger in cases with ABH than in those without ABH in both group A and B, but the differences were not significant. In males of group A, a slightly higher value was found for cases with multiple ABH, but it was slightly lower in the total cases with ABH than in cases without ABH. Thus, there was no definite correlation between smoking index and ABH occurrence in males.

Table 11. Comparative incidences of ABH of the lung from the literature

Investigators	No. of cases	Sex	No. of sections per case	Incidence of ABH (%)			
				Ca. +[a]		Ca. −[b]	
				by case	by section	by case	by section
Yanagisawa (1959)	140[c]	M & F	–	–	–	3.6	–
Morinaga and Shimosato (1987)	203[d]	–	–	13.9	–	9.6	–
Kodama et al. (1988)	131[d]	–	4–14	12.2	–	–	–
Present authors	210[d]	M & F	51	16.4	0.7	4.4	0.2
	131	Male	55	20.0	0.7	4.8	0.1
	79	Female	45	9.1	0.9	4.0	0.4

[a] Patients with primary lung cancer
[b] Patients without primary lung cancer
[c] Autopsy
[d] Surgery

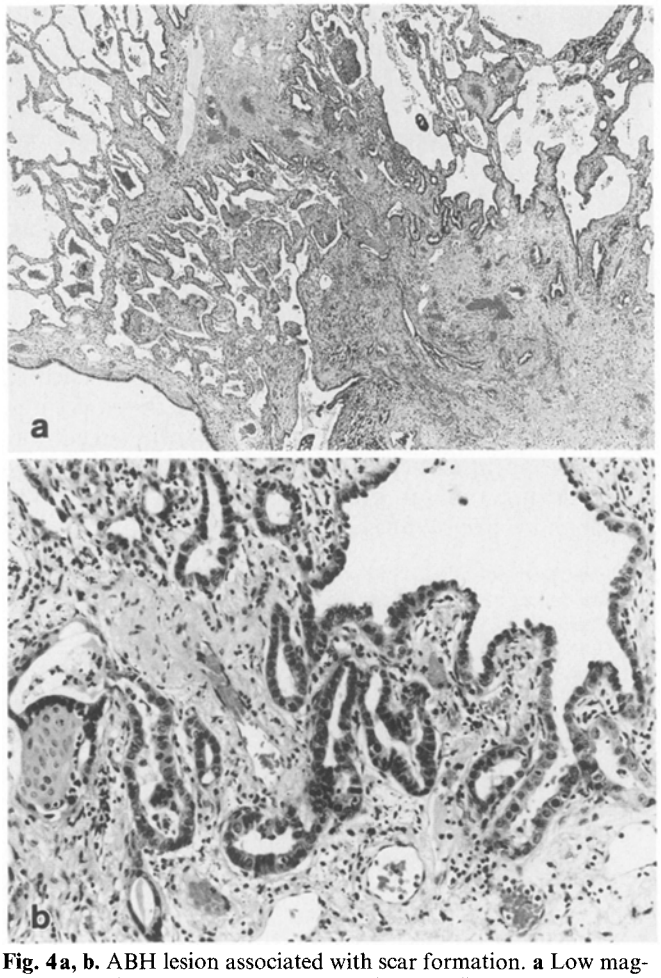

Fig. 4a, b. ABH lesion associated with scar formation. **a** Low magnification view, H & E, ×24. **b** High magnification view. Note cuboidal cells lining the markedly thickened septa

There were 8 cases which had ABH in slices in which the largest diameter of tumour was recorded (Table 9). With regard to the location of these ABHs, their distance from the tumours varied from case to case with lesions scattered throughout the peripheral tissue. There was no tendency for ABH to arise particularly near the tumour.

Out of 67 ABHs, 38 lesions were examined by elastic van Gieson staining (Table 10). Although elastosis was apparent in 34 of them, independent of size, fibrosis was recognized in only 14 lesions and in only 3 out of the 13 smallest lesions (23.1%). Only 2 lesions were found to be associated with definite scars. One of them was observed at the periphery of a squamous cell carcinoma and is illustrated in Fig. 4a and b.

Discussion

We used group B as a control group for analysis of the incidence of ABH because the lungs resected for pulmonary metastasis were not influenced by infection or pre-operative treatment, whereas autopsy lungs were usually modified by infection, irradiation and/or chemotherapy.

The present study demonstrated significant differences in association between ABH incidence and primary lung cancer when compared with secondary metastatic lung tumour. Information was also generated regarding the possible influence of other factors.

For example, the mean age of group A was higher than that of group B in both sexes and ABH-positive cases were slightly older than those without ABH. This might, in part, explain the differential in ABH incidence. However, with regard to subtypes of lung cancer, a reverse association was found for females, and the age distributions of cases with ABH in males were almost same for each histological type, despite the statistically significant differences in the incidence of ABH. We therefore consider that age might be one factor related to ABH development, but it is clearly not the major one contributing to differences in the incidences of ABH in groups A and B, or among histological subtypes of lung cancer.

With regard to smoking, a possible positive association was found for ABH in females, but this was not clear for males. Further investigation is needed to clarify this matter, but smoking does not seem to be a major factor in ABH development, in contrast to the situation with squamous metaplasia of the central bronchi, where occurrence has been reported to increase progressively with smoking exposure (Auerbach et al. 1957).

Despite differences in analytical methods, several authors reporting on the incidence of ABH have found higher values in primary lung cancer than non-primary lung cancer groups, as summarized in Table 11. In the present study, the results were generally in line with those published previously (Morinaga and Shimosato 1987; Kodama et al. 1988). However, the incidence of ABH in the primary lung cancer group was higher in this study than in the other investigations, presumably because our study was more detailed, the average number of sections examined per case being about 51. In addition, other investigators did not pay attention to sex, an important consideration, because the incidence of histological subtypes of lung cancer differs with sex. When the incidence in adenocarcinoma was compared, there was a discrepancy in that it was higher in males than in females when analysed by case and almost the same with both sexes when examined by section (Table 3). However, exclusion of the case demonstrating an extremely high number of ABHs shown in Table 6 would give an incidence of ABH by section in females of 0.2% in place and 0.9% and therefore lower than in males. Thus, the incidence of adenocarcinoma associated with ABH was considered to be higher in males than in females.

In relation to the association between ABH and histological subtype of carcinoma, other investigators have reported incidences by case of 18.8–19.2% for adenocarcinomas and 5.9–11.1% for squamous cell carcinomas (Morinaga and Shimosato 1987; Kodama et al. 1988). In this study, the incidence by section was also higher in the adenocarcinoma (0.8%) than squamous cell carcinoma (0.2%) categories, and the difference was significant. The incidence of ABH together with large cell car-

cinoma, on which no other author commented, was also higher than with squamous cell carcinoma. Further, it should be stressed that significantly higher incidences were recognized with adenocarcinomas and large cell carcinomas than with metastatic tumours.

The incidence of grade II ABH in association with adenocarcinoma was low. This may be related to difficulties in distinguishing ABHs from possible metastatic lesions in several cases of well-differentiated lung adenocarcinoma. In such cases classification of the lesions as "metastasis" was preferred. The high incidence of grade II ABH by section in the large cell carcinoma case seemed to be partly due to the fact that multiple lesions were more frequent than with the other histological types (Table 6).

Multiple ABH occurred more frequently in the adenocarcinoma and large cell carcinoma categories than with tumours of other histologies. In an extreme example, 14 ABHs were detected in 1 female case of adenocarcinoma, while multiple lesions were seen only in 1 of the metastatic lung tumour cases. Additional data are, however, required to clarify association of multiple ABH with different tumour types, especially in females.

A number of studies have related development of adenocarcinomas to ABH. For example, Yanagisawa (1959) observed highly atypical bronchioloalveolar cell hyperplasia which might be considered sufficiently atypical to be diagnosed as early adenocarcinoma. Meyer and Liebow (1965) reported that adenocarcinomas were frequently present accompanied by extensive atypical hyperplasia. Others have suspected the possiblity that some adenocarcinomas might be derived from ABH on the basis of morphometric data (Kodama et al. 1986). Furthermore, one recent report of an immunohistochemical study detailed a bronchioloalveolar carcinoma which could have arisen from ABH (Weng et al. 1990).

In the present study, while we confirmed a higher incidence of ABH in association with adenocarcinomas and large cell carcinomas than with metastatic tumours or squamous cell carcinomas, the incidence was rather low, if it is to be considered as a potential precursor for adenocarcinoma. This is particularly apparent when comparison is made with squamous metaplasia (82.8–91.2%) of the major bronchi in cases of squamous or small cell carcinoma (Auerbach et al. 1957; Tsuchiya et al. 1987). With regard to this problem, the comparatively low incidence of ABH in the present study might have derived from the relatively limited examination including only slices of S^1, S^{1+2} and S^6 and that with the largest diameter of tumour. It is therefore possible that the incidence in adenocarcinoma might be higher if the whole lung could be examined. It is noteworthy that, though only in a few cases, markedly atypical bronchioloalveolar cell hyperplasias were multifocal. This finding might throw some light on the development of multiple primary adenocarcinomas, again at low incidence (Sugimura et al. 1987).

The possible relationship between ABH and large cell carcinoma, suggested by the present findings, might support the hypothesis that adenocarcinomas and large cell carcinomas are histogenetically linked. Thus about one-half of large cell carcinomas were considered, on ultrastructural grounds, to be differentiating into adenocarcinomas (Churg 1978; Shimosato 1983; Kodama et al. 1985).

Earlier studies concentrated attention on the development of lung cancers in relation to scars (Raeburn and Spencer 1953; Lüders and Themel 1954) or honeycombing (Meyer and Liebow 1965). However, there were only 2 ABHs associated with scarring in the present series and no ABH was observed with honeycombing. Moreover, the positive rate of fibrosis in ABH was low in the smallest lesions and progressively increased with size. These results are therefore in line with the conclusion drawn earlier that most adenocarcinomas develop without a pre-existing scar, and agree with the suggestion that scarring in association with adenocarcinoma may occur during tumour growth (Shimosato et al. 1980; Madri and Carter 1984; Kung et al. 1985).

Acknowledgements. This work was supported in part by Grants-in-Aid for cancer research from the Ministry of Education, Science and Culture of Japan. The authors thank Dr. T.M. Kung, Department of Anatomical Pathology, Royal Melbourne Hospital, Australia, for linguistic assistance.

References

Auerbach O, Gere JB, Forman JB, Petric TG, Smolin HG, Muehsam GE, Kassonny DY, Stout AP (1957) Changes in the bronchial epithelium in relation to smoking and cancer of the lung. N Engl J Med 256:97–104

Churg A (1978) The fine structure of large cell undifferentiated carcinoma of the lung. Evidence for its relation to squamous cell carcinomas and adenocarcinomas. Hum Pathol 9:143–156

Honda K, Matsui Y, Sato A, Izumi T, Kobara Y, Oshima S (1983) Regional distribution of lung cancer (in Japanese with abstract in English). Haigan (Lung Cancer) 23:11–21

Kodama T, Shimosato Y, Koide T, Watanabe S, Teshima S (1985) Large cell carcinoma of the lung: ultrastructural and immunohistochemical studies. Jpn J Clin Oncol 15:431–441

Kodama T, Biyajima S, Watanabe S, Shimosato Y (1986) Morphometric study of adenocarcinomas and hyperplastic epithelial lesions in the peripheral lung. Am J Clin Pathol 85:146–151

Kodama T, Nishiyama H, Nishiwaki Y, Takanashi K, Kuroki M, Hayashibe A, Nukariya N, Kitaya T, Matusuyama T (1988) Histopathological study of adenocarcinoma and hyperplastic epithelial lesion of the lung (in Japanese with abstract in English). Haigan (Lung Cancer) 28:325–333

Kung ITM, Lui IOL, Loke SL, Khin MA, Mok CK, Lam WK, So SY (1985) Pulmonary scar cancer. A pathological reappraisal. Am J Surg Pathol 9:391–400

Lüders CJ, Themel KG (1954) Die Narbenkrebse des Lungen als Beitrag zur Pathogenese des peripheren Lungencarcinoms. Virchows Arch A Pathol Anat 325:499–551

Madri JA, Carter D (1984) Scar cancers of the lung: origin and significance. Hum Pathol 15:625–631

Meyer EC, Liebow AA (1965) Relationship of interstitial pneumonia, honeycombing and atypical epithelial proliferation to cancer of the lung. Cancer 18:322–351

Miller RR, Nelems B, Evans KG, Müller NL, Ostrow DN (1988) Glandular neoplasia of the lung. A proposed analogy to colonic tumors. Cancer 16:1009–1014

Morinaga S, Shimosato Y (1987) Microcancer of the bronchus and lung: pathology of the microadenocarcinoma in the periphery of the lung (in Japanese). Pathol Clin Med 5 [Suppl] 74–80

Morita T, Sugano H (1990) A statistical analysis of lung cancer registered in the annual of pathological autopsy cases in Japan

between 1958 and 1987, with special reference to the characteristics of lung cancer in Japan. Acta Pathol Jpn 40:665–675

Nakagawa K, Kinoshita I, Matsubara T, Tsuchiya E (1978) Metastatic pulmonary tumors. Factors affecting prognosis after pulmonary resection for metastatic pulmonary tumor. Jpn J Cancer Clin 24:1106–1112

Percy C, Sobin L (1983) Surveillance, epidemiology, and end results lung cancer data applied to the World Health Organization's classifications of lung tumors. J Natl Cancer Inst 70:663–666

Raeburn C, Spencer H (1953) A study of the origin and development of lung cancer. Thorax 8:1–10

Shimosata Y (1983) Lung cancer: on the histogenesis, differentiation and factors of prognosis (in Japanese). Trans Soc Pathol Jpn 72:29–57

Shimosato Y, Hashimoto T, Kodama T, Kameya T, Suzuki A, Nishiwaki Y, Yoneyama T (1980) Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 4:365–373

Sugimura H, Watanabe S, Tsugane S, Morinaga S, Yoneyama T (1987) Case-control study on histologically determined multiple primary lung cancer. J Natl Cancer Inst 79:435–441

Tanaka I, Matsubara O, Kasuga T, Takemura T, Inoue M (1988) Increasing incidence and changing histopathology of primary lung cancer in Japan. A review of 282 autopsied cases. Cancer 62:1035–1039

Tsuchiya E, Concetti HF, Wakimoro J, Kitagawa T, Nakagawa K, Kinoshita I, Sugano H (1982) Time trend data of histological subtypes of lung cancer cases operated and non-operated at the Cancer Institute Hospital from 1961 to 1978 (in Japanese with abstract in English). Jpn J Cancer Clin 28:196–203

Tsuchiya E, Kitagawa T, Oh S, Nakagawa K, Matsubara T, Kinoshita I, Sugano H (1987) Incidence of squamous metaplasia in large bronchi of Japanese lungs: relation to pulmonary carcinomas of various subtypes. Jpn J Cancer Res (Gann) 78:559–564

Valaitis J, Warren S, Gamble D (1981) Increasing incidence of adenocarcinoma of the lung. Cancer 47:1042–1046

Weng SY, Tsuchiya E, Satoh Y, Kitagawa T, Nakagawa K, Sugano H (1990) Multiple atypical adenomatous hyperplasia of type II pneumonocytes and bronchiolo-alveolar carcinoma. Histopathology 16:101–103

WHO (1981) Histological typing of lung tumors, 2nd edn, WHO, Geneva

Yanagisawa M (1959) A histopathological study of proliferative changes of the epithelial components of the lung. A contribution to the histogenesis of pulmonary carcinoma (in Japanese). Jpn J Cancer Clin 5:667–680