

Atypical adenomatous hyperplasia of the lung: a clinicopathological study of 118 cases including cases with multiple atypical adenomatous hyperplasia

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Abstract

Background—Atypical adenomatous hyperplasia (AAH) of the lung is a putative precursor lesion of adenocarcinoma, according to many immunohistochemical and genetical studies, but few clinicopathological studies on a large number of cases have been reported. The aim of this study was to clarify the clinicopathological characteristics of lung cancer patients with AAH lesions.

Methods—A retrospective study was carried out on 508 consecutive primary lung cancer patients operated on at National Cancer Center Hospital East. The relationship between the number and location of AAH lesions and the clinicopathological features of the lung cancer patients was analysed statistically.

Results—A total of 311 AAH lesions were found in 118 (23.2%) of the 508 cases. AAH lesions were detected in 121 of 572 lobes examined, usually in both upper lobes, and occurred most frequently in patients with adenocarcinoma (OR 2.97; 95% CI 1.82 to 4.85). AAH lesions were more frequently detected in patients with multiple primary carcinomas than in those with a single carcinoma (OR 3.06; 95% CI 1.56 to 6.00). The presence of AAH lesions was not significantly correlated with sex, age, smoking status, familial history of malignancy, or preceding malignancy. Patients with multiple AAH lesions were found to have a significantly higher frequency of preceding malignancies.

Conclusions—The present study highlights the clinicopathological characteristics of AAH lesions, showing them to be significantly associated with both adenocarcinoma and multiple primary carcinoma of the lung and suggesting common factors in the histogenesis of multiple AAH lesions and preceding malignancy.

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Keywords: atypical adenomatous hyperplasia; lung cancer; precancerous conditions

Atypical adenomatous hyperplasia (AAH) is a solitary lesion in which atypical bronchioloalveolar cuboidal cells proliferate along the alveolar septa. The morphological similarity between AAH and bronchioloalveolar carcinoma (BAC) suggested the hypothesis that

AAH is a precursor lesion of BAC.¹⁻⁶ Recent molecular genetic analyses demonstrating that some genetic abnormalities frequently detected in BAC are also observed in AAH suggest an AAH-BAC sequence in the carcinogenic pathway.^{4 7-10}

The number of AAH lesions detected dramatically increased after the introduction of helical computed tomographic (CT) health check ups in Japan,¹¹ and cases of multiple AAH lesions have also frequently been found.¹² However, fewer clinicopathological studies have been conducted on cases of AAH.^{1 13 14} We previously reported a study of 137 cases of AAH in which we found no significant correlation between the presence of AAH lesions and the outcome of patients with lung cancer.¹⁵ Based on that study, we decided to investigate the background of AAH, especially multiple AAH lesions, in greater detail. The aim of the present study was therefore to clarify the detailed clinicopathological characteristics of lung cancer patients with AAH lesions in more than 100 cases.

Methods

Between January 1995 and July 1998 508 patients underwent resection of primary lung carcinoma at the National Cancer Center Hospital East. Cases of partial resection and segmentectomy of the main tumour were excluded from the study. The lung cancers were histologically typed according to the World Health Organization classification of lung tumours.¹⁶

The resected specimens were fixed with 10% formalin or 99.8% methanol directly through the bronchial tree or pleura and the specimens were sliced at 5-10 mm intervals. We first carefully examined the entire surface of the sliced specimens with a loupe and stereoscopic microscope. The slice containing the largest diameter of the main tumour was trimmed into blocks, and any other nodular lesions detected by careful macroscopic observation were also trimmed into blocks. In addition, 1-6 random blocks from the remaining lung tissue were also trimmed. The number of sections examined ranged from 6 to 47. The mean (SD) number of blocks per patient was 16 (7). The tissue blocks were processed according to standard procedures for the preparation of haematoxylin and eosin stained histological sections and examined microscopically. A histological diagnosis of AAH was made independently by two observers (RN, TY) based on the following

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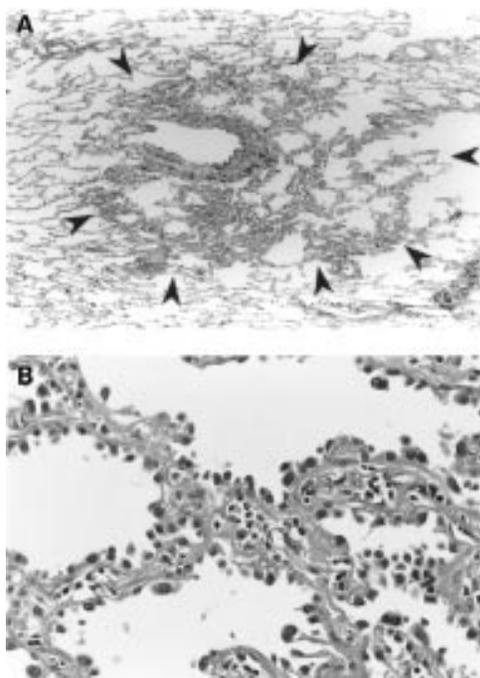


Figure 1 Pathological findings in atypical adenomatous hyperplasia (AAH). (A) The lesion has well defined boundaries (arrowhead) and the alveolar wall shows slight thickening, but there is no central scar formation or collapse. (B) Atypical cuboid to low columnar cells have proliferated along the slightly thickened alveolar wall. Atypical cells in AAH have hyperchromatic nuclei and vague or occasionally prominent nucleoli. Original magnifications (A) $\times 25$, (B) $\times 50$.

criteria^{2 15 17-19}: (1) lesion with well defined boundaries comprising a single layer of atypical cells without central scar formation or collapse; (2) abundant cytoplasm with cells which often had a rounded or domed appearance resembling type II pneumocytes; (3) atypical cells with hyperchromatic nuclei and vague or occasionally prominent nucleoli, but milder atypia than in adenocarcinoma; (4) the alveolar septa lined by atypical cells were slightly thickened by fibrosis in most instances (fig 1A and B). Two observers independently examined the specimens and discussed the cases in which their diagnoses differed. Ultimately, the diagnosis was determined based on the above criteria.

The number and location of all AAH lesions and the primary carcinomas were investigated separately in each case. In the 11 cases of central type lung carcinoma the carcinomas were

Table 1 Location of carcinomas and AAHs in each lobe

Side	No. of lobes examined	No. of carcinomas*	No. of AAH lesions	Frequency (%)†
Right				
Upper lobe	167	169	132	41 (25)‡
Middle lobe	56	29	14	6 (11)‡
Lower lobe	110	120	61	20 (18)
Left				
Upper lobe	137	135	63	35 (26)
Lower lobe	102	90	41	19 (19)
Central				
All lung fields	572	554	311	121 (21)

AAH = atypical adenomatous hyperplasia.

*Eleven were classified as central type because they could not be classified to specific lobes.

†Frequency (%) = number of lobes in which AAH was present per number of lobes examined.

‡Statistically significant difference between right upper lobe and middle lobe (OR 2.7; CI 1.1 to 6.0) using logistic regression.

classified as central lesions, but the number and location of their AAH lesions were classified as AAH lesions in each lobe in which they were detected. Cases with solitary AAH lesions were assigned to the AAH (+) group. The cases with carcinomas contiguous to AAH-like lesions without any isolated AAH were not included in the AAH (+) group. Cases without solitary AAH lesions were assigned to the AAH (-) group. To clarify the clinicopathological characteristics of the cases with multiple AAH lesions we divided the AAH (+) group into a single AAH (+) group, consisting of cases with one AAH lesion, and a multiple AAH (+) group, consisting of cases with two or more AAH lesions. We statistically analysed the correlation between the AAH groups and the following clinicopathological features: sex, age, smoking status, familial history of malignancy, preceding malignancy, histological type of primary carcinoma, and the number of primary carcinomas. Smoking status was obtained from a questionnaire on smoking habits and patients were classified as never smokers, ex-smokers, or current smokers with an estimate of the number of pack-years. A family history of malignancy and preceding malignancy was obtained from the data from the patient and family interview. We asked whether any first degree relatives (parents, children, and siblings) had a history of malignant disease.

Fisher's exact test, the χ^2 test, Student's *t* test, Mann-Whitney test, and logistic regression were used for the statistical analysis. A *p* value of 0.05 or less was considered significant.

Results

A total of 311 AAH lesions were identified in 118 (23.2%) of the 508 surgically resected cases. The mean (SD) number of blocks per patient in the AAH (+) group and AAH (-) group were the same (16 (7)).

Table 1 shows the location of primary lung carcinomas and AAH lesions in the resected lobes. A total of 543 carcinomas were detected in 572 resected lobes. Eleven carcinomas were classified as central lesions according to location. Histologically, the 554 consisted of 362 adenocarcinomas, 133 squamous cell carcinomas, 17 large cell carcinomas, 14 small cell carcinomas, and 28 adenosquamous carcinomas. Carcinomas and AAH lesions were most frequently located in the upper lobes. The frequency of AAH lesions in the right middle lobe was significantly lower than that in the right upper lobe. In six cases of multiple AAH lesions two or more lobes were resected, and five of the cases were found to have AAH lesions in two or more lobes.

Table 2 shows the number of carcinomas and AAH lesions per case. The mean number of carcinomas per case in the AAH (+) group was significantly higher than that in the AAH (-) group (1.19 *v* 1.06; *p*=0.001) The mean number of AAH lesions per case in all of the cases was 0.61, and in the AAH (+) group it was 2.64.

Table 3 summarises the relationship between the clinicopathological features of the 508

Table 2 Number of carcinomas and AAH lesions per case

Group	No. of cases	Total no. of carcinoma	No. of carcinoma/case	Total no. of AAH	No. of AAH/case
Total	508	554	1.09	311	0.61
AAH (+)	118	141	1.19*	311	2.64
AAH (-)	390	413	1.06*	0	0

AAH = atypical adenomatous hyperplasia

*p=0.001 (Mann-Whitney test).

cases in the AAH groups. The most frequent histological type of primary carcinoma in the AAH (+) group, including cases with both single and multiple AAH lesions, was adenocarcinoma (81.4%, OR 2.97; 95% CI 1.82 to 4.85). In the multiple AAH (+) group the frequency of adenocarcinoma was 89.4%, which was higher than that in the AAH (-) group and in the single AAH (+) group. Multiple primary carcinomas were detected in 35 cases, 16 of which were in the AAH (+) groups (six in the single AAH (+) group and 10 in the multiple AAH (+) group). AAH lesions were detected significantly more frequently in the patients with multiple primary lung carcinoma (OR 3.06; 95% CI 1.56 to 6.00). No significant differences in sex, age, and smoking status were observed between the AAH (-) group, the single AAH (+) group, and the multiple AAH (+) group.

Table 4 shows the combinations of histological types of multiple primary lung carcinomas in the AAH (-) group, the single AAH (+) group, and the multiple AAH (+) group. All 16 cases in the AAH (+) groups had at least one adenocarcinoma, and all 10 cases in the multiple AAH (+) group had multiple primary adenocarcinomas.

The incidence of a family history of malignancy, of lung cancer, and preceding malignancy in the three groups is summarised in table 5. There was at least one cancer patient among the first degree relatives in 39% of the primary lung cancer patients (196 of 508) but

Table 3 Relationship between clinicopathological features and AAH groups

Features	Total	AAH(-)	AAH(+) (single/multiple)	OR (95% CI)*
No of cases	508	390	118 (71/47)	
Sex				
Male	324	257	67 (38/29)	1.47 (0.97 to 2.24)
Female	184	133	51 (33/18)	
Age (years)				
≥65	252	193	59 (38/21)	1.02 (0.68 to 1.54)
<65	256	197	59 (33/26)	
Smoking status				
Never smokers	167	127	40 (26/14)	1.06 (0.69 to 1.64)
Smokers	341	263	78 (45/33)	
Ex-smokers	128	100	28 (16/12)	
≤20 pack-years smoked	29	19	10 (4/6)	
>20 pack-years smoked	99	81	18 (12/6)	
Current smokers	213	163	50 (29/21)	
≤20 pack-years smoked	17	11	6 (4/2)	
>20 pack-years smoked	196	152	44 (25/19)	
Histology†				
Adenocarcinoma	328	232	96 (54/42)	2.97 (1.82 to 4.85)
Non-adenocarcinoma	180	158	22 (17/5)	
Squamous	122	110	12 (9/3)	
Large cell	17	15	2 (1/1)	
Small cell	13	12	1 (1/0)	
Adenosquamous	28	21	7 (6/1)	
No. of lung carcinoma				
Single	473	371	102 (65/37)	3.06 (1.56 to 6.00)
Multiple	35	19	16 (6/10)	

AAH = atypical adenomatous hyperplasia.

*AAH (-) group v AAH (+) groups (logistic regression).

†In cases of multiple carcinoma the histological type of the largest tumour was used.

Table 4 Combination of multiple primary carcinomas (n=35) and AAH groups

No. of carcinomas	Histological combination	AAH group	
		AAH (-)	AAH (+) Single Multiple
2	Ad/Ad	5	4 7
	Ad/Sq	5	1 0
	Sq/Sq	4	0 0
	Ad/Sm	1	0 0
	Sq/Sm	1	0 0
3	Ad/Ad/Ad	1	0 1
	La/Sq/Sq	1	0 0
4	Ad/Ad/Ad/Ad	1	1 2

AAH = atypical adenomatous hyperplasia; Ad = adenocarcinoma; Sq = squamous cell carcinoma; La = large cell carcinoma; Sm = small cell carcinoma.

Table 5 Relationship between familial history, preceding malignancy and AAH groups

Features	Total	AAH(-)	AAH(+) (single/multiple)	OR (95% CI)†
Family history of malignancy				
(+)	196	147	49 (30/19)	1.17 (0.77 to 1.79)
(-)	312	243	69 (41/28)	
Family history of lung carcinoma				
(+)	40	26	14 (7/7)	1.88 (0.96 to 3.71)
(-)	468	364	104 (64/40)	
Preceding malignancy				
(+)	41	27	14 (3/11*)	1.81 (0.92 to 3.55)
(-)	467	363	104 (68/36*)	

AAH = atypical adenomatous hyperplasia.

*Statistically significant compared with AAH (-) group (OR 4.11; 95% CI 1.98 to 8.53) and single AAH (+) group (OR 6.93; 95% CI 2.08 to 23.06) by logistic regression.

†AAH (-) group v AAH (+) groups by logistic regression.

there was no significant correlation between a family history of malignancy and the presence of AAH. In 40 of the 196 cases there was a family history of lung cancer; 14 of the cases were in the AAH (+) group and 26 in the AAH (-) group but there was no significant correlation between a family history of lung cancer and the AAH groups. In contrast to the family history of malignancy, 11 cases (23.4%) in the multiple AAH (+) group had a preceding malignancy of their own. A significant correlation between a history of preceding malignancy and multiple AAH lesions was observed. The preceding malignancies in the 11 cases in the multiple AAH (+) group consisted of two cases of gastric cancer, three cases of colorectal cancer, and one case each of cancer of the liver, breast, urinary bladder, thyroid, head and neck, and malignant lymphoma. Most of the preceding malignancies had been diagnosed and cured at other hospitals, so we were unable to confirm the histological type of the preceding malignancy.

Discussion

We have analysed 508 surgically resected cases of lung cancer, with or without solitary AAH lesions; 118 (23.2%) of the 508 cases were found to have solitary AAH lesions. We have previously reported AAH lesions in 16 of 241 elderly necropsy cases (6.6%) and found them to be more frequent in 12 of 118 patients with a malignant neoplasm (11.1%).¹⁹ In this study the occurrence of AAH lesions in lungs surgically resected for cancer was higher than in the previous study, suggesting that AAH occurs more frequently in lung cancer patients.

In this study the clinicopathological results clearly show a close correlation between the presence of AAH lesions and both adenocarcinoma and the occurrence of multiple primary cancers. Our findings are consistent with the hypothesis that AAH is a precursor of adenocarcinoma of the lung.^{1 2 13 14} They are important because they confirm the concept of the progression of multistep carcinogenesis through AAH to adenocarcinoma of the lung. We and other investigators have also provided evidence of a sequence from AAH to adenocarcinoma. We previously reported the monoclonal nature of AAH based on an X chromosome-linked polymorphic marker, the human androgen receptor gene (HUMARA).²⁰ Immunohistochemical studies of carcinoembryonic antigen (CEA) and the p53 gene product combined with molecular genetical analysis of the p53 gene have shown that the immunohistochemical and genetic abnormalities frequently observed in adenocarcinoma are also detected in AAH lesions.^{4 20-23} These findings, combined with the results of the present study, strongly support the hypothesis that an AAH to adenocarcinoma sequence is one of the carcinogenetic pathways in the lung.

The clinical management of AAH lesions has not yet been determined. In this study we have shown that AAH lesions are closely associated with multiple adenocarcinoma and that they are evenly distributed throughout the whole lung, although AAH lesions were observed less frequently in the middle lobe than in the other lobes. These findings indicate the possibility that the risk of metachronous lung adenocarcinoma is higher in patients with multiple AAH lesions. In fact, we encountered one case of metachronous primary lung adenocarcinoma in which there were multiple adenocarcinomas and multiple AAH lesions. Thus, close and precise follow up is necessary for patients with multiple AAH lesions.

To identify patients with multiple AAH lesions we examined a mean of 16 (7) blocks per patient. Chapman *et al* also reported finding AAH lesions in about 30% of patients with adenocarcinoma of the lung by examining 1–6 random sampling blocks of lung parenchyma.²⁴ These data, combined with the findings in our present study, suggest that careful observation of all surfaces of sliced specimens with a loupe and stereoscopic microscope is important to detect these small lesions.

A family history of malignancy and of lung cancer were not significantly correlated with the AAH (–) group, single AAH (+) group, or multiple AAH (+) group. On the other hand, the cases with multiple AAH lesions were shown to have a higher frequency of preceding malignancy throughout the whole body, although the organ affected by the preceding malignancy was not specifically correlated with AAH. This suggests that patients with multiple AAH lesions may have a predisposition to malignant neoplasms. In the near future it will be possible to diagnose AAH lesions preoperatively by advanced radiological imaging. Precise whole body examinations will therefore be

possible in patients with multiple AAH lesions. However, the process of progression of AAH remains unclear. Further prospective follow up studies will be needed to establish a method of management for patients with AAH.

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