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Prognostic Suggestion in the Evaluation of Solid Component in Poorly Differentiated Adenocarcinoma of the Lung

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Abstract

Pulmonary adenocarcinoma composed of pure or predominant solid components is reported to be a highly malignant tumor. However, the existence of solid components and its connection with biological behavior have not been well documented. To answer this question, we histologically subclassified poorly differentiated adenocarcinoma (P/D Ad Ca) into solid type and non-solid type, and compared the biological behavioral characteristics.

Material and Methods: All histological specimens of surgically resected primary lung carcinoma diagnosed as P/D Ca or large cell carcinoma in Nippon Medical School Hospital were re-evaluated according to the 1999 WHO manual. The cases re-evaluated as P/D Ad Ca were further divided into solid type and non-solid type according to our original definition: the solid type contains solid components where a glandular structure is not recognized in more than one high-power field, while in the non-solid type, a small glandular structure is observed in every high-power field. The differences in the occurrence of lymph node metastasis were assessed by Fisher's exact test.

Results: Among 109 cases satisfying both histological and clinical investigation, 45 cases were re-evaluated as P/D Ad Ca; solid type ($n=22$), and non-solid type ($n=23$). Lymph node metastases occurred at a higher rate in the solid type than in the non-solid type ($p<0.01$).

Conclusion: Patients with solid type Ad Ca have reached a more advanced stage than patients having non-solid type due to high metastatic rate to lymph nodes. These results suggest that we should not overlook solid components even if the solid components are the focal lesion. This sub-typing alerts clinicians to survey metastases, and may contribute to therapeutic strategies in the future. (J Nippon Med Sch 2003; 70: 28–33)

Key words: lung, adenocarcinoma, lymph node, metastasis, solid

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Introduction

Compared with pulmonary squamous cell carcinoma, pulmonary adenocarcinoma is on the increase in Japan and Western countries[1-3]. Simultaneously, many investigations into the prognostic factors of adenocarcinoma have been published. For instance, the expression of P 53[4], angiogenesis[5] seems to be related to poor prognosis, and tumors with elastosis[6], small or lesser fibrosis[7], or the expression of bcl-2[4] are reported to indicate favorable prognosis. These published data are useful, but obtaining many of these markers requires special procedures other than the everyday conventional methods used for histological diagnosis.

Poorly differentiated adenocarcinoma (P/D Ad Ca) is reported to be related to poor prognosis[8-10]. In lung carcinoma, the histological type of solid Ad Ca with mucin is reported as one predictor of unfavorable prognosis[11-13], but when the P/D component is mixed with other more differentiated types, the question of whether the existence of the P/D component itself relates to poor prognosis or not still remains uncertain. In the thyroid, papillary carcinoma with a P/D component has a poorer prognosis than that without a P/D component[10]. We hypothesized that there is P/D Ad Ca of the lung which relates to prognosis, and reached the subtyping of P/D Ad Ca. In this study, we assumed that prognosis-related histology had to be easily recognizable by conventional stainings.

Materials and Methods

Materials

All cases of surgically resected primary lung cancers that had been classified as poorly differentiated pulmonary carcinoma (P/D Ca) or as large cell carcinoma (LCC) in the medical records of Nippon Medical School Hospital between 1976 and 1998 were reviewed. In these cases, initial histological diagnoses of the operated tumors were made in accordance with the General Rules for Clinical and Pathological Records of Lung Cancer in Japan current at the time of each diagnosis, which were modified versions of the former WHO classification[14,15]. One hundred and twenty-eight cases were recorded as P/D Ca or LCC. Cases of death within 30 days of the operation and/or cases without specimens were excluded from the study. One hundred and nine cases were qualified for further histologic re-evaluation.

Methods

Histological re-classification

All histological specimens in each case were basically composed of cut surfaces of the primary tumor and dissected lymph nodes, and the number of cut surfaces depended on the maximum diameter of the tumor. All hematoxylin and eosin stained slides were re-evaluated with light microscopy by one medical student (E.S.) and three pathologists (M. K., T.N., and S.K.). Some additional slices of paraffin blocks were stained with alcian blue-periodic acid Schiff with or without diastase digestion and/or mucicarmine to identify epithelial mucin. Revision of the original diagnosis was made according to the criteria of the 1999 WHO classification[16]. Histological grade was determined by the most poorly differentiated component[16]. In this study, we accepted the WHO criteria when the most poorly differentiated component occupied 10% or more of the tumor. Therefore, if the poorly differentiated component comprised 10% of the whole tumor, it would be classified as P/D Ca even though 90% of the tumor was well differentiated. After completing our revisions, we further sub-divided P/D adenocarcinoma (P/D Ad Ca) into two sub-types: solid type and non-solid type. In this study, the solid type was defined as containing solid components, where a glandular structure is not recognized in more than one high-power field, while the non-solid type was defined as having one or more small glandular structure in every high-power field (**Fig. 1**). High power view observations showing samples with comedo type necrosis or scirrhous type morphology led to the exclusion from the solid type.

Statistical analyses

According to the UICC: TNM classification[17], the difference in the incidence of lymph node metastasis

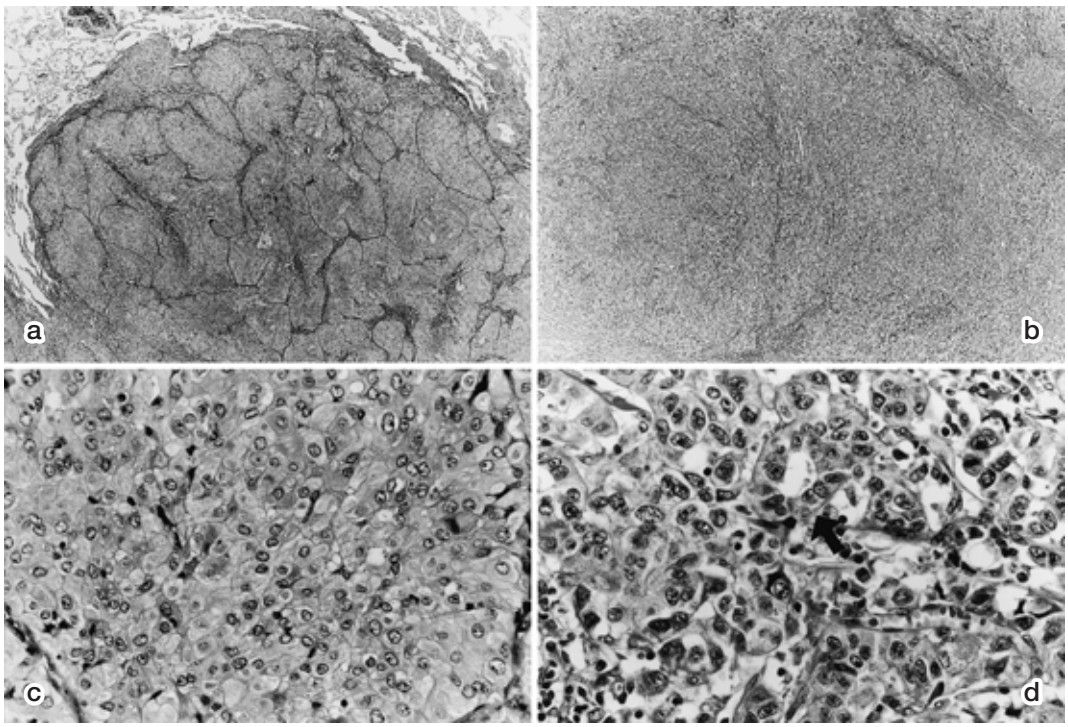

Fig. 1 Subtyping of poorly differentiated adenocarcinoma of the lung. a, c) Solid type. b, d) Non-solid type.
a, b) Low power magnification views show no apparent differentiation of adenocarcinoma. (original magnification ×40)
c, d) High power magnification view (×400). c) Glandular structure is not observed in this view. d) Small glandular structure (arrow) is observed.

in the T factor between the solid type and non-solid type was assessed by Fisher's exact test. The survival curves were drawn in relation to solid type and non-solid type by the Kaplan-Meier method. The survival term was calculated from the date of operation to the date of the most recent follow-up examination or to the date of death. The difference between survival curves was measured using the logrank test. A probability of less than 0.05 was accepted as statistically significant.

Results

Among the 128 cases recorded as P/D Ca or LCC, 6 cases of operative death, and 13 cases without paraffin block were excluded from further elucidation. Thus, 109 cases were available for re-evaluation. Histological diagnoses at the time of operation were as follows: P/D Ad Ca (n=44); P/D squamous cell carcinoma (SqCC) (n=43); LCC (n=18); adenosquamous carcinoma (AdSq Ca) (n=2); Large cell neuroendocrine carcinoma (LCNEC) (n=1); and giant cell carcinoma (n=1).

The results of histological re-evaluation were as follows: P/D Ad Ca (n=45); P/D SqCC (n=19); LCC (n=15); AdSqCa (n=2); LCNEC (n=2); pleomorphic carcinoma (n=2); combined LCC (n=2); giant cell carcinoma (n=2); unclassified carcinoma (n=1); moderately differentiated adenocarcinoma (n=6); moderately differentiated squamous cell carcinoma (n=11); well differentiated adenocarcinoma (n=1); and sclerosing hemangioma (n=1).

Forty-five cases were re-evaluated as P/D Ad Ca because the P/D component occupied 10% or more of the tumor, and none of these cases was purely occupied by the P/D component. In other words, all of these cases had differentiated areas of adenocarcinoma. Thus, special staining for the detection of epithelial mucin was basically used for the diagnosis of other histological classifications such as SqCC and LCC in which no epithelial mucin was identified.

Sub-classification of P/D Ad Ca

Among the 45 cases of re-classified P/D Ad Ca, 22 cases were sub-classified as solid type, and 23 cases were sub-classified as non-solid type, according to our definition given in the materials and methods section and **Fig. 1**. The overall characteristics of adenocarcinoma of solid type and of non-solid type based on several clinicopathologic features are shown in **Table 1**. The survival rate of both types was the same (p=0.9554 analyzed by logrank test). Mediastinal lymph node dissection was performed for all these cases, and the incidence of lymph node metastasis in the group of solid type Ad Ca was higher significantly than in the group of non-solid type Ad Ca (p=0.0023) (**Table 2**). Analysis of each T stage in lymph node metastasis showed significant differences between solid and non-solid type tumors in T 2 cases (p=0.0198). Among the T 2 cases, the distribution of the cases with pleural (p 2) or subpleural (p 1) involvement and the cases without visceral pleural involvement (p 0) was as follows: p 2 (n=1); p 1 (n=3); p 0 (n=4) in solid type. In non-solid type, it was p 2 (n=2); p 1 (n=3); p 0 (n=7).

Table 1 Patient characteristics in poorly differentiated pulmonary adenocarcinoma

		Solid	Non-solid
Number of patients		22	23
Sex	Male	16	17
	Female	6	6
Age	mean±S.D.	59.9±10.2	62.7±12.0
	range	38—77	31—83
Stage Ⅰ		2	11
Stage Ⅱ		2	4
Stage ⅢA		11	3
Stage ⅢB		6	0
Stage Ⅳ		1	5

Solid=Solid type
Non-solid=Non-solid type
S.D.=Standard deviation

Discussion

Regarding lung carcinoma, solid carcinoma with mucus formation (this histological sub-type is equivalent to solid adenocarcinoma with mucin in the latest WHO criteria) is one of the independent predictors of poor prognosis[11-13]. Kwiatkowski et al. reported that the cancer-free survival rate of stage I patients having solid carcinoma with mucus formation was significantly shorter than in other histological types[11]. In the WHO criteria, solid adenocarcinoma with mucin is a tumor purely composed of solid components without any other differentiation[16]. However, as we showed in our results, we encountered no patients having solid adenocarcinoma with mucin out of approximately 100 P/D carcinomas. Rainio et al. also reported that among 61 patients with adenocarcinoma, only one was diagnosed as having solid adenocarcinoma with mucin[18]. These facts indicate that solid adenocarcinoma with mucin is rare, and the concept that this type is one of the predictors of recurrence is not practically useful for many patients with lung adenocarcinoma.

Table 2 Lymph node metastatic features of solid type versus non-solid type poorly differentiated adenocarcinoma of the lung in relation to T factors

	Lymph node metastasis	solid	non-solid	p Value
T1	Positive	3	1	p>0.9999
	Negative	2	2	
T2	Positive	7	3	p=0.0198
	Negative	1	9	
T3	Positive	2	2	p>0.9999
	Negative	1	3	
T4	Positive	6	2	p=0.3333
	Negative	0	1	
all T factors	Positive	18	8	p=0.0023
	Negative	4	15	

T= T factor of the primary tumor

In following papers, tumors have been divided according to the predominant histology. Sørensen et al. reported that patients with solid carcinoma with mucus formation had the poorest prognosis compared with all other subtypes[12,13]. Classification depending on predominant histology may be worthwhile; however, if the tumor had solid components but the predominant histology was not solid carcinoma with mucin, such tumors would be divided into histological types other than solid carcinoma with mucus formation. In other words, if the tumor contains solid parts as a minor component, its solid part would be ignored. As a result, this histological typing is not as valuable as ours, because we showed that tumors having solid components played an important role in themselves in the high metastatic rate to lymph nodes.

We demonstrated that high rate lymph node metastasis occurred especially in solid type T 2 cases. Kawahara et al. reported that the incidence of lymph node metastasis was high in tumors with pleural (p 2) or subpleural (p 1) involvement[19]. In this regard, we examined pleural involvement, and as shown in our results, then determined that there was no apparently biased distribution of pleural involvement between solid type and non-solid type. Thus, our results suggest that there are many cases with lymph node metastasis in solid type, although the size of the primary tumor is small.

In the thyroid, papillary carcinoma is known to be a tumor with favorable prognosis, but when a non-glandular component is present, the prognosis of papillary carcinoma is worsened[10]. Moreover, in most cases of P/D Ca of the thyroid, the P/D area (non-glandular component) does not dominate the tumor, and the existence of this minor component makes the prognosis worse[10]. Our results in pulmonary solid type P/D Ad Ca only showed a high metastatic rate to lymph nodes, and our results on survival term showed no difference compared with non-solid type. However, the facts concerned with thyroid carcinoma suggest that solid type P/D Ad Ca of the lung may also be related to the poor prognosis. Further investigation of a large number of cases will clarify this question.

In conclusion, we emphasize that we should not classify tumors according to their predominant part. Rather, we should observe whether tumors have poorly differentiated components or not, because this relates to lymph node metastasis and may relate to prognosis. The subclassification of solid type is also useful in practical medicine, because this classification is based on hematoxylin and eosin stains without using any special techniques such as immunohistochemistry. Awareness of high metastatic rates to lymph nodes makes it possible to alert clinicians to the necessity of surveying metastasis more carefully, and may contribute to therapeutic strategy in the future.

The question of why P/D Ad Ca having solid components show high metastatic rates to lymph nodes is unsolved. Further elucidation including the difference in gene expression between the solid and non-solid type will clarify this morphology-related biological behavior.

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