Expression of adhesion molecules and transforming growth factor-β in pleomorphic carcinomas of the lung

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Abstract. Pleomorphic carcinoma (PC) of the lung consists of an epithelial component showing the histology of poorly differentiated non-small cell carcinoma of the lung and a sarcomatous component, that is more aggressive compared to non-small cell carcinoma of the lung. To determine the differences between an epithelial component of PC and poorly differentiated non-small cell carcinoma, the expression of adhesion molecules (E-cadherin, β-catenin and N-cadherin) and transforming growth factor-β (TGF-β) was compared immunohistochemically among 14 poorly differentiated adenocarcinomas of the lung (PDAs) and 14 PCs of the lung, with an epithelial component, showing the histology of PDA. Expression levels of E-cadherin and β-catenin were significantly lower in epithelial or sarcomatous components of PCs than in PDAs while that of TGF-β was significantly higher in epithelial components of PCs than in PDAs. No significant difference was found in incidences of the expression of these molecules between epithelial and sarcomatous components of PCs. No significant difference was noted in the expression level of N-cadherin among PDAs and epithelial and sarcomatous components of PCs. The present results showed that E-cadherin and β-catenin expression is reduced and TGF-β expression is increased in epithelial components of PCs with the same histology as PDA when compared to PDAs, suggesting that an epithelial component of PC is distinct from non-small cell carcinoma with the same histology.

Introduction

Pleomorphic carcinoma (PC) of the lung, one of the sarcomatoid carcinomas (1), comprises both an epithelial component and a sarcomatous component of spindle and/or giant cells or of spindle or giant cells only and an aggressive cancer, with the prognosis of PCs as well as sarcomatoid carcinomas being worse than that of non-small cell carcinomas (2,3). The epithelial component of PC shows the same histology as poorly differentiated non-small cell carcinoma of the lung (1). Przygodzki *et al* (4), however, showed that mutation frequencies and patterns for p53 and K-*ras* were different between the epithelial components of PCs and non-small cell carcinomas, indicating that epithelial components of PCs are distinct from poorly differentiated non-small cell carcinomas. However, the differences between an epithelial component of PC and a corresponding poorly differentiated non-small cell carcinoma have yet to be clarified.

Cell adhesion molecules are expressed in various types of cancer and their altered expression is associated with the dedifferentiation, invasion and metastasis of cancer cells (5-8). E-cadherin forms a calcium-dependent cell-cell adhesion complex together with β-catenin which binds to the intracellular domain of E-cadherin as well as actin filaments, connecting this adhesion complex to the cell cytoskeleton (5-8). The E-cadherin-β-catenin complex is essential for the formation of stable cell-cell adhesion and its reduced expression has been shown to be associated with dedifferentiation, metastasis and poor prognosis in various types of cancer including lung cancer (5-8). On the other hand, the up-regulated expression of N-cadherin, another calcium-dependent adhesion molecule, has been shown to be associated with the invasive and metastatic potential of cancers (9-12). It has been shown that the overexpression of N-cadherin increases the migration, invasion and metastasis of breast cancer cells through the N-cadherin-mediated interaction of cancer to stromal cells (10).

Cancer cells of an epithelial cell phenotype often change into fibroblast-like cells expressing a mesenchymal cell phenotype. This phenomenon, known as epithelial-mesencymal transition, promotes the invasion and metastasis of cancer cells (13-15). Transforming growth factor (TGF)-β is one of the epithelial-mesencymal transition-inducing factors (14,16,17). TGF-β has been reported to be associated with poor prognosis of patients with certain types of cancer including lung cancer (18-22).

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Key words: pleomorphic carcinoma, lung, E-cadherin, β-catenin, transforming growth factor-β

Table I. Antibodies used for the immunohistochemistry analysis.

Antigen	Clone	Source	Dilution	Antigen retrieval
Pankeratin	Polyclonal	Dakocytomation, Glostrup, Denmark	1:500	Protease
EMA	E29	Dakocytomation, Glostrup, Denmark	1:80	None
CEA	Polyclonal	Dakocytomation, Glostrup, Denmark	1:1000	None
E-cadherin	36B5	Novocastra, Newcastle upon Tyne, UK	1:50	MW
β-catenin	17C2	Novocastra, Newcastle upon Tyne, UK	1:80	MW
N-cadherin	IAR06	Novocastra, Newcastle upon Tyne, UK	1:100	MW
TGF-β	TGFB17	Novocastra, Newcastle upon Tyne, UK	1:40	MW

EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; TGF-β, transforming growth factor-β; MW, microwave.

Table II. Clinical findings of 14 patients with pleomorphic carcinomas.

Patient	Age (years)	Gender	Location	Size (mm)	pStage	Treatment	Histology		E/S percentage	Follow-up
							E	S		
1	74	M	LLL	47x63x70	IIIa	Lob.+Rad.	PDA	Spindle	20/60	11 mo.dead
2	71	M	RUL	42x23	IV	Lob.	PDA	Spindle	80/20	5 mo.dead
3	58	M	RML	90x76	IIb	Lob.	PDA	Spindle+giant	40/60	3 mo.alive
4	52	M	LUL	32x30	IIIa	Lob.+Che.	PDA	Spindle	80/20	11 mo.dead
5	70	M	RLL	45x23	Ib	Lob.	PDA	Spindle+giant	20/80	2 mo.dead
6	75	M	RUL	60x50	IIb	Lob.	PDA	Spindle+giant	10/90	6 mo.dead
7	68	M	LUL	80	IIb	Lob.+Che.	PDA	Giant	10/90	3 mo.dead
8	76	M	LUL	40x30x35	IIIa	Lob.+Rad.	PDA	Giant	10/90	11 yr.dead
9	67	M	RUL	45x30x48	IIb	Lob.	PDA	Spindle	20/80	5 mo.dead
10	69	M	LLL	50x30	IIb	Lob.	PDA	Spindle+giant	10/90	3 mo.alive
11	44	M	LUL	72x65x70	IIb	Lob.+Rad.	PDA	Spindle+giant	20/80	9 mo.dead
12	48	M	LUL	60x55x80	IIb	Lob.+Che	PDA	Spindle+giant	10/90	7 mo.alive
13	64	M	LUL	72x46	IIb	Lob.	PDA	Spindle+giant	20/80	6 mo.dead
14	41	M	LUL	35x25x30	IIb	Lob.+Che.	PDA	Giant	20/80	6 mo.dead

M, male; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; Lob., lobectomy; Rad., radiation; Che., chemotherapy; Spindle, Spindle cell type; giant, giant cell type; mo., months; yr., years; E, epithelial component; S, sarcomatous component; PDA, poorly differentiated adenocarcinoma.

To elucidate the differences between an epithelial component of PC and a corresponding poorly differentiated non-small cell carcinoma, the expression of the above-mentioned molecules was investigated immunohistochemically in poorly differentiated adenocarcinomas of the lung and PCs with an epithelial component exhibiting the same histology as poorly differentiated adenocarcinoma.

Materials and methods

Subjects. A total of 14 PC specimens and 14 specimens of poorly differentiated adenocarcinomas were used for this study. The specimens were obtained from lung tissues resected at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. Written consent was obtained from each patient prior to the operation and the anonymous usage of tissue samples for pathological studies was permitted. This study was approved by the Ethics Committee of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. The PC specimens contained epithelial and sarcomatous components; the epithelial components showed a histology of poorly differentiated adenocarcinoma. Poorly differentiated adenocarcinomas 1, 6, 1, 5 and 1 were at pStages Ia, Ib, IIa, IIb and IV, respectively.

Immunohistochemistry. Details of the primary antibodies used and their dilutions are shown in Table I. Immunohistochemical staining was performed using formalin-fixed, paraffin-embedded tissue sections with an EnVision detection system (EnVision$^+$; Dakocytomation, Glostrup, Denmark). The sections were deparaffinized and rehydrated, and endogenous peroxidase activity was blocked using 0.03% H_2O_2.

Table III. Expression of epithelial markers and vimentin in pleomorphic carcinomas and poorly differentiated adenocarcinomas of the lung.

	Cytokeratin		EMA		CEA		Vimentin	
Case	E	S	E	S	E	S	E	S
Pleomoprhic carcinoma								
1	(-)	(-)	(3+)	(3+)	(3+)	(-)	(2+)	(3+)
2	(3+)	(3+)	(3+)	(1+)	(-)	(-)	(-)	(2+)
3	(3+)	(-)	(-)	(-)	(-)	(-)	(-)	(3+)
4	(3+)	(3+)	(3+)	(3+)	(3+)	(-)	(-)	(3+)
5	(3+)	(3+)	(-)	(-)	(3+)	(2+)	(-)	(3+)
6	(3+)	(3+)	(3+)	(-)	(3+)	(2+)	(-)	(3+)
7	(3+)	(2+)	(3+)	(3+)	(-)	(-)	(-)	(3+)
8	(3+)	(-)	(3+)	(2+)	(1+)	(-)	(-)	(2+)
9	(3+)	(-)	(-)	(-)	(2+)	(1+)	(-)	(3+)
10	(3+)	(3+)	(3+)	(3+)	(-)	(-)	(-)	(3+)
11	(3+)	(2+)	(3+)	(2+)	(-)	(-)	(-)	(3+)
12	(3+)	(2+)	(3+)	(2+)	(-)	(-)	(-)	(3+)
13	(3+)	(3+)	(3+)	(3+)	(3+)	(2+)	(-)	(3+)
14	(-)	(3+)	(3+)	(3+)	(-)	(-)	(-)	(-)
Poorly differentiated adenocarcinoma								
1	(1+)		(3+)		(1+)		(-)	
2	(3+)		(3+)		(3+)		(-)	
3	(3+)		(3+)		(3+)		(-)	
4	(3+)		(3+)		(2+)		(-)	
5	(3+)		(3+)		(2+)		(-)	
6	(3+)		(3+)		(1+)		(-)	
7	(3+)		(3+)		(-)		(-)	
8	(3+)		(3+)		(1+)		(-)	
9	(3+)		(-)		(-)		(-)	
10	(3+)		(3+)		(3+)		(-)	
11	(3+)		(3+)		(2+)		(-)	
12	(3+)		(3+)		(3+)		(-)	
13	(3+)		(3+)		(1+)		(-)	
14	(3+)		(3+)		(3+)		(-)	

EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; E, epithelial component; S, sarcomatous component. Staining grade: (-), positive cells (p)≤5%; (1+), 5%<p≤30%; (2+), 30%<p≤70%; (3+), p>70%.

The tissue sections were then incubated with the primary antibody (Table I). After washing with TBS (0.01 M Tris buffered saline, pH 7.4), the sections were incubated with the peroxidase-labeled polymer from an EnVision+ system (Dakocytomation) and the color reactions were obtained with 3,3'-diaminobenzidine (Dakocytomation). For the antigen retrieval of E-cadherin, β-catenin, N-cadherin and TGF-β, the sections were subjected to microwave treatment for 15 min with 0.05 M Tris buffer (pH 9.0). For the antigen retrieval of cytokeratin, the sections were incubated with 0.05% protease (Protease type XXIV) (Sigma, St. Louis, MO, USA) at 37˚C for 30 min and then boiled twice for 5 min each time in 0.01% citrate buffer (pH 6.0). The immunostain was graded according to the proportion of positive cells (p), as follows: (-), p≤5%; (1+), 5%<p≤30%; (2+), 30%<p≤70%; (3+), p>70%.

Statistical analysis. Immunohistochemical positive staining was analyzed using the λ^2 test using Stat Mate III for Windows software (ATMS, Tokyo, Japan). Significance was defined as $p<0.05$.

Results

Clinical findings. Table II shows a clinical summary of the PC patients. The patients were male, ranging in age from 41 to 76 years (mean 62.6). PCs 1, 9, 3 and 1 were at pStages Ib, IIb, IIIa and IV, respectively. The patients underwent lobectomy, with 3 and 4 patients receiving radiation therapy and chemotherapy, respectively, in addition to the lobectomy. Of the 14 patients, 11 succumbed to the disease during the follow-up period, 10 patients succumbed within 11 months

Table IV. Expression of adhesion molecules and TGF-β in pleomorphic carcinomas and poorly-differentiated adenocarcinomas of the lung.

	E-cadherin		β-catenin		N-cadherin		TGF-β	
Case	E	S	E	S	E	S	E	S
Pleomorphic carcinoma								
1	(-)	(-)	(3+)	(-)	(-)	(-)	(3+)	(2+)
2	(-)	(-)	(-)	(-)	(-)	(-)	(2+)	(+)
3	(-)	(-)	(3+)	(1+)	(2+)	(1+)	(-)	(-)
4	(2+)	(1+)	(-)	(-)	(-)	(-)	(3+)	(3+)
5	(3+)	(1+)	(3+)	(1+)	(-)	(2+)	(2+)	(2+)
6	(-)	(-)	(-)	(1+)[a]	(-)	(1+)	(-)	(-)
7	(-)	(-)	(-)	(-)	(-)	(-)	(2+)	(2+)
8	(2+)	(-)	(-)	(-)	(-)	(-)	(3+)	(1+)
9	(-)	(-)	(-)	(-)	(3+)	(3+)	(-)	(1+)
10	(1+)	(-)	(-)	(-)	(2+)	(2+)	(-)	(-)
11	(-)	(-)	(-)	(-)	(-)	(-)	(2+)	(-)
12	(1+)	(-)	(-)	(-)	(-)	(-)	(2+)	(2+)
13	(3+)	(-)	(-)	(-)	(-)	(-)	(1+)	(-)
14	(-)	(-)	(3+)	(-)	(1+)	(-)	(3+)	(2+)
Poorly differentiated adenocarcinoma								
1	(3+)		(3+)		(2+)		(2+)	
2	(3+)		(3+)		(-)		(-)	
3	(3+)		(3+)		(-)		(-)	
4	(2+)		(3+)		(-)		(-)	
5	(3+)		(2+)		(-)		(-)	
6	(3+)		(3+)		(-)		(2+)	
7	(-)		(3+)		(-)		(1+)	
8	(3+)		(2+)		(-)		(1+)	
9	(3+)		(3+)		(-)		(-)	
10	(3+)		(3+)		(-)		(-)	
11	(3+)		(3+)		(-)		(-)	
12	(3+)		(3+)		(-)		(-)	
13	(3+)		(3+)		(-)		(-)	
14	(3+)		(3+)		(-)		(1+)	

TGF-β, transforming growth factor-β; E, epithelial component; S, sarcomatous component. Staining grade: (-), positive cells (p)<5%; (1+), 5%<p≤30%; (2+), 30%<p≤70%; (3+), p>70%. [a]Nuclear staining.

after the lobectomy regardless of pStage and 1 patient succumbed 11 years after the lobectomy.

Histological findings. The histology of the PCs is shown in Table II. Epithelial components of the PCs consisted of poorly differentiated adenocarcinoma (Fig. 1A). Sarcomatous components of 4, 3 and 7 PCs contained spindle tumor cells only (Fig. 1B), giant tumor cells only (Fig. 1C) and spindle and giant tumor cells, respectively.

Immunohistochemical findings. Table III shows the expression of epithelial markers such as cytokeratin, EMA and CEA, as well as a mesenchymal marker, vimentin, in PCs and poorly differentiated adenocarcinomas. Cytokeratin, EMA and CEA were expressed in epithelial components of 12, 11 and 7 of 14 PCs, respectively. The epithelial components of the PCs expressed cytokeratin or EMA. The expression of vimentin was found in the epithelial component of 1 of 14 PCs. Cytokeratin, EMA and CEA were expressed in sarcomatous components of 10, 10 and 4 of 14 PCs. Sarcomatous components of 12 of 14 PCs expressed cytokeration or EMA. Sarcomatous components of PCs except one PC expressed cytokeration, EMA or CEA. Cytokeratin, EMA and CEA were expressed in 14, 13 and 12 of 14 poorly differentiated adenocarcinomas. Vimentin was not expressed in all poorly differentiated adenocarcinomas. The expression of adhesion molecules and TGF-β in PCs and poorly differentiated adenocarcinomas is shown in Table IV. Positive staining of E-cadherin, β-catenin

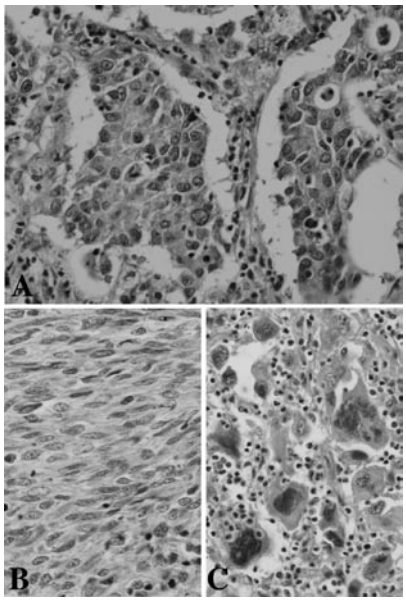

Figure 1. Epithelial and sarcomatous components of a pleomorphic carcinoma. Hematoxylin and eosin staining. Magnification, x400. (A) An epithelial component showing the histology of poorly differentiated adenocarcinoma. (B) spindle cells and (C) giant cells in a sarcomatous component are shown.

and N-cadherin was found on the membrane of tumor cells (Fig. 2), whereas TGF-β was positively stained in the cytoplasm of tumor cells (Fig. 3). A sarcomatous component of one PC only showed both membranous and nuclear staining of β-catenin. Table V shows the comparison of incidences of the expression of adhesion molecules and TGF-β at the 2+ and 3+ staining grades among epithelial and sarcomataous components of PCs and poorly differentiated adenocarcinomas. The incidences of the expression of E-cadherin and β-catenin at the 2+ and 3+ staining grade are significantly higher in poorly differentiated adenocarcinomas than in epithelial or sarcomatous components of PCs. The incidence of the expression of TGF-β at the 2+ and 3+ staining grades was significantly lower in poorly differentiated adenocarcinomas than in epithelial components of PCs. No significant difference in the expression of E-cadherin, β-catenin and TGF-β at the 2+ and 3+ staining grades was found between sarcomatous and epithelial components of PCs. No significant difference was noted in an incidence of the expression of N-cadherin at the 2+ and 3+ staining grades among poorly differentiated adenocarcinomas and epithelial and sarcomatous components of PCs.

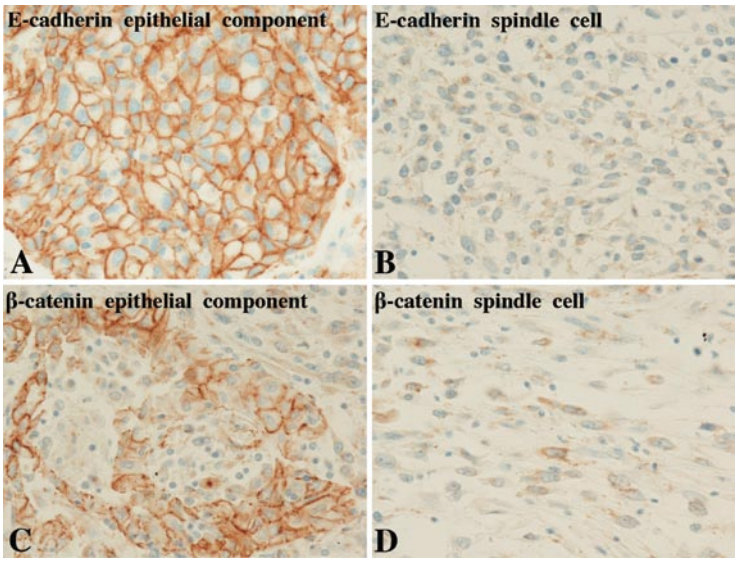

Figure 2. Immunohistochemical stain for E-cadherin and β-catenin. Magnification, x400. (A) and (C) Positive staining for E-cadherin and β-catenin in epithelial components of PCs, respectively. (B) and (D) Positive staining for E-cadherin and β-catenin in sarcomatous components of PCs, respectively. Staining grades for A, B, C and D are 3+, 1+, 3+ and 1+, respectively.

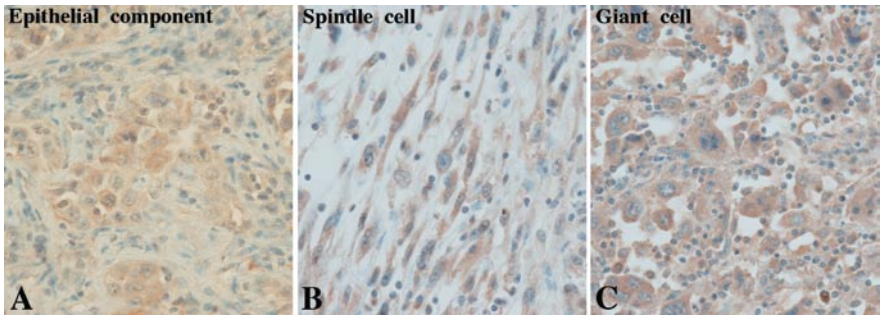

Figure 3. Immunohistochemical stain for TGF-β. Magnification, x400. (A), (B) and (C) Positive staining for TGF-β at the staining grade 3+ in an epithelial component of a PC, and spindle and giant cells in sarcomatous components of PCs, respectively.

Table V. Expression of adhesion molecules and TGF-β at 2+ and 3+ staining grades in pleomorphic carcinomas and poorly differerentiated adenocarcinomas of the lung.

	Pleomorphic carcinoma		Poorly differentiated adenocarcinoma
	Sarcomatous component	Epithelial component	
E-cadherin	0/14 (0%)	4/14 (28.6%)	13/14 (92.9%)
	NS	p<0.05	
	p<0.05		
β-catenin	0/14 (0%)	4/14 (28.6%)	14/14 (100%)
	NS	p<0.05	
	p<0.05		
N-cadherin	3/14 (21.4%)	3/14 (21.4%)	1/14 (7.14%)
	NS	NS	
	NS		
TGF-β	6/14 (42.9%)	9/14 (64.3%)	2/14 (14.3%)
	NS	p<0.05	
	NS		

TGF-β, transforming growth factor-β; NS, not significant.

Discussion

The follow-up data of the PC patients showed that 10 of 11 patients who died of PC succumbed to the disease within a year after the lobectomy and one patient succumbed 11 years after the lobectomy. The follow-up data confirmed poor prognosis of patients with PCs, as previously reported (2,3).

A sarcomatous component of PC is considered to represent the sarcomatous change of cancer cells in an epithelial component (1). This change is supported by the immunohistochemical and ultrastructural identification of epithelial features in a sarcomatous component and by identical gene mutations in epithelial and sarcomatous components (1,23). The immunohistochemical results of the present study also confirmed the expression of epithelial markers, such as cytokeratin, EMA and CEA, in sarcomatous components in 13 of 14 PCs, thus supporting the epithelial origin of tumor cells in a sarcomatous component of PC.

It has been reported that the N-cadherin expression is uncommon in adenocarcinomas of the lung and is not a prognostic factor thereof (24,25). In the present study, incidences of N-cadherin expression were also low in poorly differentiated adenocarcinomas, as well as in epithelial and sarcomatous components of PCs. Additionally, no significant difference was noted in the N-cadherin expression among the adenocarcinomas and components of PC. These results suggest that the aggressiveness of PCs is not associated with N-cadherin expression.

The E-cadherin and β-catenin expression was reduced, while the TGF-β expression was increased in epithelial and sarcomatous components of PCs compared to poorly differentiated adenocarcimonas, although the epithelial components of PCs showed the same histology as poorly differentiated adenocarcinomas. Numerous studies showed that the loss or reduction of the E-cadherin-β-catenin complex is associated with metastasis and a poor prognosis in non-small cell carcinomas of the lung (5,6,26,27). Moreover, the TGF-β expression was reported to be associated with poor prognosis of patients with adenocarcinomas of the lung (18,19). Therefore, the reduced expression of E-cadherin and β-catenin and the increased expression of TGF-β in PCs appear to be associated with the aggressiveness of PCs. Furthermore, although the histology is the same, the different expression of the three molecules between epithelial components of PCs and poorly differentiated adenocarcinomas appears to reflect their different nature. On the other hand, TGF-β has been reported to be an inducing factor of the epithelial-mesenchymal transition in which cancer cells lose the epithelial phenotype and acquire the

mesenchymal phenotype, thereby becoming more aggressive (13-17). Therefore, TGF-β may play a role in the generation of spindle or giant cells in a sarcomatous component from cancer cells in an epithelial component in PCs.

Przygodzki *et al* (4) showed that mutation frequencies and patterns for p53 and K-*ras* were different between the epithelial components of PCs and non-small cell carcinomas, indicating that PC is distinct from non-small cell carcinoma of the lung. In agreement with this study, the present results showed that the expression of E-cadherin, β-catenin and TGF-β was different between poorly differentiated adenocarcinomas and the epithelial components of PCs showing the same histology as poorly-differentiated adenocarcinoma. It is generally accepted that a sarcomatous component of PC develops from an epithelial component of PC (1,23). However, PC is not a tumor of non-small cell carcinoma of the lung with a sarcomatous change.

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