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Lung carcinoma with rhabdoid component. A series of seven cases associated with uncommon types of non-small cell lung carcinomas and alveolar entrapment

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Summary. Rhabdoid tumor, included in the WHO classification among large cell carcinomas of the lung, is an uncommon type of lung carcinoma with poor prognosis.

We report a series of 7 cases of lung carcinomas with rhabdoid component in 10% and 80% of the tumor. The associated tumor was adenocarcinoma in 3 cases - one of them with focal micropapillary pattern - large cell carcinoma in 2 cases, squamous cell carcinoma in 1 case and pleomorphic carcinoma in 1 case. Two adenocarcinomas showed a focal spindle cell component. Micropapillary and pleomorphic types had not been reported before as a component associated with rhabdoid carcinomas. All cases were positive for vimentin, and AE1/AE3 cytokeratin and 5 cases for cytokeratin 7. All cases were negative for muscle and endothelial markers and for chromogranin A. Synaptophysin was focally positive only in one case.

Alveolar trapping inside the tumor was present in 3 cases - a phenomenon not well studied in lung carcinomas and also not reported in tumors with rhabdoid component.

Five patients died because of the tumor within 2 to 31 months after diagnosis, one of myocardial infarction and only one is alive and disease free 123 months after the diagnosis.

In summary, we describe 7 new cases of this uncommon lung tumor with aggressive clinical course, associated with infrequent histological types in nonrhabdoid component and with alveolar trapping, a nondescribed finding.

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Key words: Lung carcinoma, Rhabdoid, Micropapillary, Large and giant cell, Pleomorphic carcinoma, Alveolar trapping

Introduction

Rhabdoid tumor was described in 1978 by Beckwith et al. as a distinctive renal tumor in children, characterized by large cells with eosinophilic cytoplasmic globules and large eccentric nucleus with prominent nucleolus (Beckwith et al, 1978, Haas et al., 1981), which they called rhabdoid cells.

This cell morphology has also been found in other neoplasms of different sites (Ekfors et al., 1985; Small et al., 1985; Harris et al., 1987; Batsakis and Manning, 1988; Patrón et al., 1988; Carter et al., 1989; Perrone et al., 1989; Matias et al., 1990; Kodet et al., 1991; Niffenegger et al., 1992; Cattani et al., 1992; Walford et al., 1992; Chetty and Bhathal, 1993; Ueyama et al., 1993; Chang et al., 1994; Parham et al., 1994; Suárez-Vilela et al., 1996; Cavazza et al., 1996; Rubenchik et al., 1996; Chetty et al., 1997; Albores-Saavedra et al., 2000, 2007; Chetty, 2000; Miyagi et al., 2000; Attems and Lintner, 2001; Shimazaki et al., 2001; Kaneko et al., 2002; Hiroshima et al., 2003; Tamboli et al., 2004; Falconieri et al., 2005; Dundr et al., 2006; Ordoñez, 2006; Serra et al., 2006; Song et al., 2007) and of different histogenetic origins in which recognizable "parent" neoplasms (carcinoma, melanoma, sarcoma, mesothelioma) are admixed with the rhabdoid component.

Several cases have been reported in the lung (Cavazza et al., 1996; Rubenchik et al., 1996; Chetty et al., 1997; Chetty, 2000; Miyagi et al., 2000; Attems and Lintner, 2001; Shimazaki et al., 2001; Kaneko et al.,

2002; Hiroshima et al., 2003; Tamboli et al., 2004; Falconieri et al., 2005; Song et al., 2007). This entity is included in the World Health Organization classification of lung tumors in the group of large cell carcinomas (Brambilla et al., 2004).

The inclusion of alveoli inside lung tumors has been described as a way of interaction between tumor cells and lung parenchyma - basically in the periphery of the tumor (Alvarez-Fernández 1982; Dingemans and Mooi, 1986; Paakko et al., 1990; Nakanishi et al., 1996; Funai et al., 2003; Kobayashi et al., 2006; Mochizuki et al., 2008), mainly in squamous cell carcinoma but, so far, never in lung tumors with rhabdoid features.

We report seven new cases of lung carcinoma with rhabdoid features, emphasizing the poor prognosis of this neoplasm, the wide spectrum of associated histological types, its immunohistochemical features and its relationship with the alveolar inclusion.

Materials and methods

Seven lung carcinomas with rhabdoid features were identified among a series of 610 non small cell pulmonary carcinomas, 463 cases came from the Pathology files of the Department of Pathology of Gregorio Marañón Hospital (Madrid. Spain) and 147 cases came from the Department of Pathology of Vigo General Hospital (Vigo, Spain). Clinical information and follow-up data of the patients were retrieved from the clinical records. Staging of tumors was made according to the 2002 TNM staging system (Wittekind et al. 2005). A lung carcinoma was considered to show a significant rhabdoid phenotype when at least 10% of the tumor cells showed rhabdoid features (Cavazza et al., 1996; Shimazaki et al., 2001; Tamboli et al., 2004), i.e. acidophilic globular cytoplasmic inclusions.

Immunohistochemical stains were performed on formalin fixed, paraffin-embedded material in a DAKO Tech-mate 500 Autostainer, with enVision visualization system (DAKO), using the following antibodies: vimentin (clone V9, 1/1000, Novocastra, Newcastle, UK), TTF-1 (clone 8G7G3/1, 1/50, DAKO, Glostrup, Denmark), Ki67 (clone MIB-1, 1/500, DAKO), synaptophysin (polyclonal, 1/100, Novocastra), chromogranin A (clone LK2H10, 1/50, Novocastra), cytokeratin 7 (clone OV-TL, 1/50, DAKO), cytokeratin 20 (clone A103, 1/50, DAKO), AE1-AE3 cytokeratin (clone AE1/AE3, 1/500, Zymed, San Francisco, CA), smooth muscle actin (clone αsm-1, 1/100, Novocastra), desmin (clone D33, 1/50, DAKO), CD31 (JC70A, 1/25, DAKO), CD34 (clone QBEnd/10, 1/50, DAKO) and MyoD1 (CLONE 5.8A, 1/50, DAKO). Antigen retrieval with protease incubation was performed for cytokeratin 7 and cytokeratin 20 staining. Heat induced epitope retrieval in a 5 mM citrate buffer at pH6, during 2 minutes, with a pressure cooking method, was used for the other antibodies. Positive and negative tissue controls were used.

Descriptive statistics were used to describe the patients' characteristics and outcome. Categorical data are expressed as counts and proportions. Survival was defined as the interval between the date of surgery and the date of death related to lung cancer or the date of the most recent contact for censored cases. Survival probability was calculated by the Kaplan–Meier method. Due to the small number of cases, no univariate survival analysis to compare survival probabilities among different levels of categorical variable (prognostic factor) was performed.

Results

Clinical findings

Clinical data are summarized in Table 1. Patients were 5 men and 2 women, whose age ranged from 39 to 76 years (mean age: 59.5 years, median age: 60 years). Surgical resection was performed in all cases: 5 lobectomies, one of them including chest wall resection, one pneumonectomy and one wedge resection.

Tumor stage was IA in one patient, IB in three patients, IIIA in two patients and IIIB in one patient - due to the presence of another nodule in the same lobe. One patient received preoperative chemotherapy and another one adjuvant chemotherapy.

Six patients were smokers and three showed respiratory symptoms at clinical onset.

Pathologic findings (Table 1)

The resected tumors measured between 1.5 cm and 9 cms in diameter (median 4 cm). The percentage of rhabdoid component ranged from 10% to 80% (Fig 1A,B). Rhabdoid cells showed large nuclei with prominent nucleoli and paranuclear eosinophilic cytoplasmic inclusion that in some cells impinged upon the nuclei and rejected it to the periphery of the cytoplasm (Fig 1A). Associated tumor type was adenocarcinoma in 3 cases, large cell carcinoma in 2 cases, squamous cell carcinoma in one case and pleomorphic carcinoma in one case. In two adenocarcinomas, spindle cells with a sarcomatoid appearance were focally present (cases 1 and 7) (Fig. 1D) and one of them also showed focal micropapillary areas with small cellular aggregates without fibrovascular cores inside the central lumina lying in stromal gaps (Fig 1C). Three cases (2, 4 and 6), two large cell carcinomas and one squamous cell carcinoma, grew focally in the alveolar interstitium entrapping alveoli that were preserved as lumina of different sizes lined by cuboidal alveolar cells or as groups or rows of isolated elements in the periphery of the tumor cords (Fig. 1F-H). This alveolar trapping was extensive in one large cell carcinoma and in the squamous cell carcinoma, and focal in the other large cell carcinoma, at the periphery of the neoplasm.

Table 1. Clinicopathologic characteristics of the reported cases of lung carcinomas with rhabdoid features.

Reference	Case number	Sex/ age	Clinical findings	Smoking	Location/ diameter	Metastases	TNM	Lung asssociated tumor	% rhabdoid component	Follow-up (months)
Cavazza et al 1996	1	F/54	Hemoptysis	Y	RUL/NA	LN	NA	LCC	90	AWD 6
	2	M/36	Chest pain	NA	LUL/NA	NA	NA	Sarcoma	>10	AWD 4
	3	M/47	Hemoptysis	Y	RLL/NA	NA	NA	ACA	>10	DOD 4
	4	F/71	NA	NA	LUL/NA	LN	NA	ACA	10	AWD 2
	5	M/71	NA	NA	RLL/NA	NA	NA	LCC	>10	AU 5
	6	F/25	Bazex´syndrome	No	LLL/NA	LN, lung	NA	LCC	10	NA
Rubenchik et al 1996	7	M/74	Incidental	Y	LLL/3.5	NA	NA	NA	Most	ANED 24
	8	M/68	Hemoptysis, Cough	No	RML/3	LN	NA	ACA	>10	DOD 6
Chetty et al 1997	9	F/62	Hemoptysis, Cough	Y	RUL/11	Present	NA	LCNEC	25	DOD 3
	10	M/40	Chest pain, cough, dyspnea	No	RUL/6	NA	NA	ACA	>10	LFU 6
Chetty et al 2000	11	F/50	Cough, dyspnea	Y	LLL/17	LN	NA	LCNEC, SCC	15	DOD 6
	12	M/53	Hemoptysis, Cough	Y	LUL/12	NA	NA	LCNEC, SCC, SqCC	10	DOD 12
Miyagi et al 2000	13	M/51	Hemoptysis	Y	RUL/4	LN	IIIA	ACA	70	DOD 36
	14	M/72	Cough	No	RUL/5.6	LN	IIIA	ACA	90	DOD 4
	15	M/50	Fatigue	No	RML/3	NA	IA	ACA	50	AU 41
Shimazaki et al 2001	16	M/69	X-ray finding	NA	RLL/4.5	No	IIIA	PDT	18.2	DOD 1.5
	17	M/66	Hemoptysis	NA	LUL/6	No	IIIB	PDT	15.5	DOD 0.6
	18	M/82	Cough, chest pain, dyspnea	Y	LUL/11	No	IIIA	PDT	15	DOD 1
	19	F/47	Cough, hemoptysis	Y	RUL/8.5	No	IIIA	PDT	60	DOD 10
Attems et al 2001	20	F/69	Chest pain	Y	RUL/2	Duodenum, skin, adrenal	NA	Pseudomeso-theliomatous ACA	NA	Death non related disease 3
Kaneko et al 2002	21	M/59	NA	Y	RUL/4.5	Adrenal	NA	LCC	90	ANED 6
Hiroshima et al 2003	22	F/70	Incidental coin lesion	NA	LL	No	IA	LCC	30	Relapse 72
Tamboli et al 2004	23-1	M/57	Respiratory	Y	LUL/23	NA	NA	Sarcomatoid CA	25	LFU
	24-2	F/57	Hemoptysis	Y	LUL/4	Brain, jejunum	I	LCC	90	DOD 11
	25-3	M/54	Hemoptysis	Y	RUL/4	Liver, bone, LN	IV	LCC	15	DOD 4
	26-4	F/48	Hoarseness	Y	RUL/5.1	Lung, LN	IIIB	ACA	10	DOD 19
	27-5	M/54	Hemoptysis, GI bleeding	NA	RUL/10	Soft tissue, bowell, LN	IV	LCC	90	DOD 5
	28-6	M/70	Knot in right lateral chest wall	Y	Left lung/NA	Bone, chest wall	IV	ACA	90	DOD 10
	29-7	M/61	Hemoptysis	Y	RUL/4.7	LN, bone	IIIA	Sarcomatoid CA	30	DOD 15
	30-8	F/59	Cough	Y	RML/NA	Brain, bone lung, LN	IV	ACA	50	DOD 3
	31-9	M/34	Hemoptysis	NA	LLL/2	Lung	IV	Sarcomatoid CA	60	DOD 3
	32-10	M/65	Mass in the chest wall	NA	LLL/NA	Chest wall	IV	Sarcomatoid CA	75	LFU
	33-11	F/59	Hemoptysis	Y	LLL/3	LN	IIIA	ACA	20	ANED 20
Falconieri et al 2005	34-1	M/50	Chest pain	NA	RUL/8	Recent case	NA	ERC	100	ANED
	35-2	F/58	Cough, chest pain, dyspnea	NA	LLL/3	No	NA	ERC	100	ANED
	36-3	M/56	Chest pain, weight loss	NA	RLL/4	NA	NA	ERC	100	LFU
	37-4	M/63	Cough, chest pain, weight loss	NA	RUL/4.8	Brain	NA	ERC	100	AWD
Song et al 2007	38	M/59	Blood sputum, Chest discomfort	NA	RLL/10		IB	BAC, ACA	30	AWD
Present series	39-1	M/59	No	Y	LUL/3.5/C	Adrenal	IB	ACA, micropapilae, spindle cells	30	DOD 15
	40-2	M/52	Hemoptysis	Y	RLL/8/P	Lung	IIIA	pleomorphic CA, AE	80	DOD 6
	41-3	F/59	Chest pain	Y	LLL/8/P	Lung, LN, bone, liver	IIIB	ACA	50	DOD 2
	42-4	M/64	No	Y	RUL/3/P	Bone, LN, adrenal	IIIA	SqCC, AE	10	DOD 31
	43-5	M/39	Cough, Chest pain, hemoptysis	Y	RUL/9/C	No	IB	LCC	80	ANED 123
	44-6	M/68	No	Y	RUL/1.5/P	Lung, bone	IA	LCC, AE	10	DOD 23
	45-7	F/76	No	No	RUL-ML/4/C	No	IB	ACA, spindle cell	40	Death non related disease 6

LCC: large cell carcinoma. ACA: adenocarcinona. LCNEC: large cell neuroendocrine carcinoma. SCC small cell carcinoma. SqCC: squamous cell carcinoma. PDT: poorly differentiated tumor. ERC: exclusive rhabdoid carcinoma. C: central. P: peripheral. AE: alveolar entrapment. ANED: alive with no evidence of disease. AU: alive status unknown. AWD: alive with disease. DOD: dead of disease. LFU: lost for follow-up.

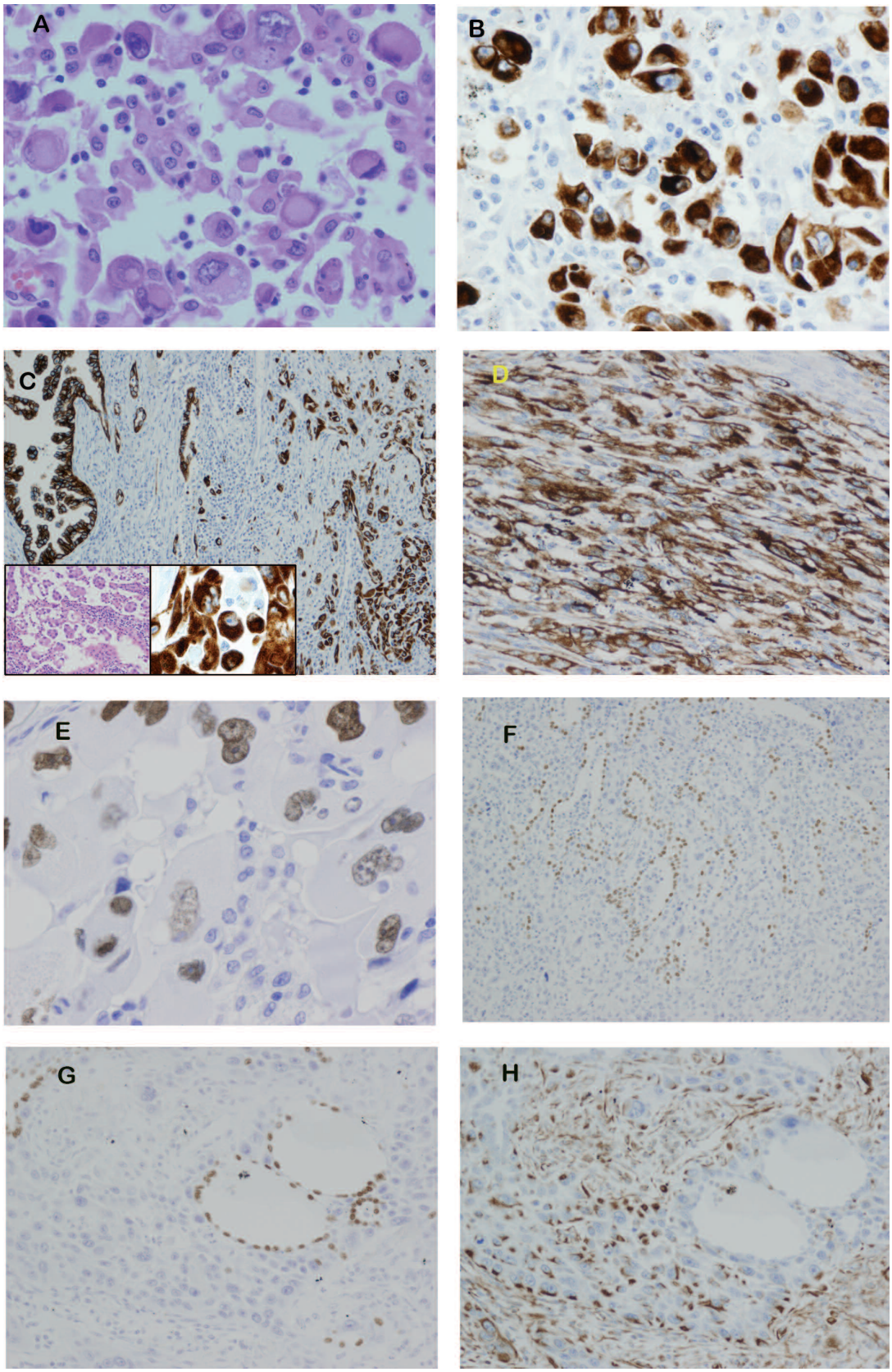

Fig. 1. A. Tumoral cells with rhabdoid features: large eccentric nuclei, prominent nucleoli and big, globulous, eosinophilic cytoplasms. (Case 2. x 400). **B.** Strong cytoplasmic stain for cytokeratins (AE1-AE3 antibody). (Case 7. x 200). **C.** Micropapillary pattern in the adenocarcinoma component (left) and rhabdoid cells (right) (AE1-AE3 antibody). Inset left: micropapillary pattern (H-E). Inset right: rhabdoid cells (enlargement of the lower right area) (AE1-AE3 antibody). (Case 1. x 40. Left inset left x 100. Right inset x 200). **D.** Spindle cells of the sarcomatoid carcinoma pattern (AE1-AE3 antibody). (Case 7. x 100). **E.** Stain for TTF1 antigen on the nuclei of tumoral cells with large, globulous, eccentric cytoplasm. (Case 7. x 400). **F.** Alveoli included inside the neoplasm. The nuclei of the pneumocytes lining the alveolar lumina are positive for TTF1. Tumoral cells are negative. (Case 2. x 100). **G and H.** Serial section of the same field. Alveoli included are lined by pneumocytes with small, uniform nuclei, positive for TTF1. The tumoral cells are negative for this marker (Fig 1G. x 200). Tumoral cells show a globular eccentric stain for Vimentin. The pneumocytes are negative (Fig 1H. x 200). (Case 4).

Table 2. Immunohistochemical results.

	Vimentin	TTF-1	KI-67	CHR	SYN	AE1-3	CK-7	CK20	CD31	CD34	MyoD1	SMA	Desmin
1	+, NR-	-, NR+		-	-	+	+, R<	-	-	-	-	-	-
2	+	-	90	-	-	+ F	-	-	-	-	-	-	-
3	+ F	-	50	-	+ F	+	+	-	-	-	-	-	-
4	+	-	30	-	-	+	+ F	-	-	-	-	-	-
5	+	-	60	-	-	+	-	-	-	-	-	-	-
6	+	-	60	-	-	+	+	-	-	-	-	-	-
7	+	+	20	-	-	+	+	-	-	-	-	-	-

SYN: synaptophysin, CHR: chromogranin A, SMA: smooth muscle actin, NR: non rhabdoid, R: rhabdoid, F: focal.

Immunohistochemical findings (Table 2)

The results of immunohistochemical staining are summarized in Table 2. The paranuclear inclusions in the rhabdoid cells stained for pancytokeratin (Fig. 1B) and for vimentin (Fig. 1H) in all 7 cases. Positive staining for CK7 was found in 5 cases (Fig. 1D). All them were CK 20 negative. TTF1 was positive in 1 case (Fig. 1E) in 60% of the nuclei, and positive in nonrhabdoid component in another one. TTF1 positive pneumocytes adherent to septal walls clearly demonstrate the interstitial growth of tumor (Fig. 1F,G) with preserved alveolar structures as was previously observed at H&E staining. In some areas these structures were partially destroyed and replaced by the tumor and they were easily demonstrated with TTF1 antibody as strands, small aggregates or even isolated alveolar cells (Fig. 1F,G). As far as neuroendocrine markers are concerned, chromogranin A was negative in all cases and synaptophysin was focally positive only in one case in non-rhabdoid areas. Muscular and endothelial markers were negative.

Clinical follow up (Table 1)

Follow up ranged between 2 and 123 months, with a median of 14.7 months and a mean of 29.3 months. Only one patient is alive and disease free. One patient died 6 months after surgery due to myocardial infarction. The other five patients died due to recurrent neoplasm. The three-year survival was 17% and the median survival was 23 months (IC 95%: 4-42 months). In these five patients, the median disease free interval was 6.8 months (range 2-16 months, mean 8 months). All of them recurred in the first two years after surgery. Recurrence was systemic in all patients involving liver, adrenals and/or bones. Five patients had lung relapse as carcinomatous lymphangitis or diseminated lung nodules.

Discussion

In this article we report seven new cases of rhabdoid carcinoma of the lung with a rhabdoid component associated with histological types not previoulsly described, such as micropapillary adenocarcinoma and pleomorphic carcinoma, and emphasize the finding of normal alveolar trapping inside the neoplasm in three cases - an uncommon characteristic not reported in lung carcinomas with a rhabdoid component till date.

Renal rhabdoid tumor was described by Beckwith et al. - from the National Wilms Tumor Study Group - as a renal tumor with a peculiar morphology, found in children and characterized by poor prognosis (Beckwith and Palmer, 1978). The hallmark of the tumor is rhabdoid cells with a globular eosinophilic cytoplasmic inclusion that displaces the nucleus to the periphery and sometimes causes nuclear indentantion (Beckwith and Palmer, 1978; Cavazza et al., 1996). Ultrastructurally, the inclusion is made up by intermediate filaments arranged in a whorl pattern (Beckwith and Palmer, 1978; Cavazza et al., 1996; Shimazaki et al., 2001; Falconieri et al., 2005). This type of cell made up the whole neoplasm in renal rhabdoid tumors of children.

Subsequently, tumors containing this type of cell have been described in extra renal locations, most of them in adults. They can be found in skin, prostate, urinary bladder, intestine, tongue, liver, soft tissue, uterus, gallbladder, brain, vulva, orbit, stomach, pancreas, thyroid, adrenal, heart, lung, melanoma and mesothelioma (Ekfors et al., 1985; Harris et al., 1987; Batsakis and Manning, 1988; Patrón et al., 1988; Small et al., 1985; Carter et al., 1989; Perrone et al., 1989; Matias et al., 1990; Cattani et al., 1992; Niffenegger et al., 1992; Walford et al., 1992; Chetty and Bhathal, 1993; Ueyama et al., 1993; Parham et al., 1994; Cavazza et al., 1996; Rubenchik et al., 1996; Suárez-Vilela et al., 1996; Chetty et al., 1997; Chetty, 2000; Miyagi et al., 2000; Attems and Lintner, 2001; Shimazaki et al., 2001; Kaneko et al., 2002). In contrast to renal rhabdoid tumors, the rhabdoid component is mixed with another identifiable cellular type in most of these extrarenal neoplasms, so that they have been called composite extrarenal rhabdoid tumors (Wick et al., 1995) or tumors with a rhabdoid phenotype (Weeks et al., 1989). In the lung, the accepted criteria to classify a tumor as having rhabdoid features or a rhabdoid phenotype is that 10% or more of the tumor cells show rhabdoid characteristics as referred to above (Cavazza et al., 1996; Shimazaki et al., 2001; Tamboli et al., 2004). The nonrhabdoid

component was large cell carcinoma or adenocarcinoma in most cases, but sarcomatoid carcinoma, bronchiolo-alveolar carcinoma, large cell neuroendocrine carcinoma, small cell carcinoma or squamous cell carcinoma have also been described (Table 1). Four cases with pure rhabdoid morphology without any specific differentiation have been reported (Falconieri et al., 2005). In four cases the rhabdoid component ranged from 10% to 80% of the tumor cells and the associated nonrhabdoid tumor was adenocarcinoma in 3 cases, large cell carcinoma in 2 cases, squamous cell carcinoma in 1 case and pleomorphic carcinoma in 1 case. Focal spindle cell component was present in two of the adenocarciomas. This spindle cell component has been found in 6 cases, including our two cases (Tamboli et al., 2004). Although the rhabdoid phenotype in lung carcinomas has been included as a type of large cell carcinoma in the WHO classification of tumors of the lung (Brambilla et al., 2004), the finding of a spindle cell component, in addition to the rhabdoid features also mimicking mesenchymal cells as its name indicates, allows the inclusion of some of these neoplasms in the group of sarcomatoid carcinomas. One adenocarcinoma also showed focal micropapillary features, a component not described before that can have a bad prognostic significance by itself (Amin et al., 2002; Sánchez-Mora et al., 2008). The pleomorphic component has not been described in carcinomas of lung with rhabdoid features either. The association with these two high grade tumor types does not seem to have been previously recognized. Therefore, carcinoma of lung with a rhabdoid phenotype is associated with a wide spectrum of other histologic variants of lung neoplasms, mainly subtypes with a poor prognosis and survival: sarcomatoid, pleomorphic and micropapillary carcinomas (Fishback et al., 1994; Rossi et al., 2003; Sánchez-Mora et al., 2008).

We report 7 new cases of lung carcinoma with rhabdoid features to be added to the 38 cases previously reported (Table 1). It is an uncommon neoplasm which is only 1.1% of the cases in our series of 640 nonsmall cell carcinomas of the lung. Miyagi et al. (2000) found three cases in their series of 902 surgically resected carcinomas (0.3%). They are the only authors reporting this incidence in a series of lung neoplasms. The age of the 45 patients ranged between 25 and 82 years (median, 59); 29 were men and 16 women. They presented with respiratory and thoracic symptoms as cough, hemoptysis, dyspnea, hoarseness and chest pain, besides weight loss, in most of cases. Twenty six were smokers. Only 6 were nonsmokers. In 13 patients this item was not recorded. The size of the tumor ranged from 1.5 cm to 23.0 cms.

Although some tumors of the lung with a rhabdoid phenotype have been described as not to express cytokeratins (Cavazza et al., 1996; Rubenchik et al., 1996; Attems and Lintner, 2001; Tamboli et al., 2004), most of them do so. Vimentin expression is constantly found (Cavazza et al., 1996; Chetty et al., 1997; Chetty, 2000; Miyagi et al., 2000; Shimazaki et al., 2001; Kaneko et al., 2002; Tamboli et al., 2004). CK7 is present in some cases (Tamboli et al., 2004; Song et al., 2007) and CK20 in none (Tamboli et al., 2004). All our cases were positive for vimentin and AE1-AE3 cytokeratin, 5 cases for CK7 and none for CK20. TTF1 is positive in 1 of our cases in nonrhabdoid component but also focally in rhabdoid cells in another case. This antibody was negative in the rhabdoid component in all of the reported cases (Tamboli et al., 2004; Falconieri et al., 2005; Song et al., 2007). However, in some tumors the nonrhabdoid component showed staining for this marker (Tamboli et al., 2004; Song et al., 2007). As far as neuroendocrine markers are concerned, whereas chromogranin A was negative in all the cases, synaptophysin was focally positive in one case. Consequently, we found neuroendocrine features focally in only one case. Several authors have reported this differentiation (Cavazza et al., 1996; Kaiserling et al., 1996; Miyagi et al.,2000; Shimazaki et al., 2001). Endothelial and myogenic phenotypes were absent.

These tumors behave aggressively and most of them are in advanced stage (III or IV) at clinical onset (Miyagi et al., 2000; Shimazaki et al., 2001; Tamboli et al., 2004) (Table 1). However, it is not certain whether these patients do worse than TNM stage–matched patients who have advanced nonsmall cell lung carcinoma (Tamboli et al., 2004). Shimazaki et al. (2001) found that the cases with more than 10% of rhabdoid cells component had a worse prognosis than the patients with less than this percentage, setting it as a criterion to define this neoplasm. Among our cases, 4 were in stage I and 3 in stage III. Five patients died of the tumor (two stage I and three stage III), one died of non related disease and only one patient was alive without disease 123 months after the resection. Therefore the clinical course is aggressive, but due to the few cases it is not statistically significant.

Alveolar inclusion inside lung tumors is a histologic phenomenon infrequently reported (Alvarez-Fernández 1982; Dingemans and Mooi, 1986; Paakko et al., 1990; Nakanishi et al., 1996; Funai et al., 2003; Kobayashi et al., 2006; Mochizuki et al., 2008); most of the reports included a small number of cases. It is more common in squamous cell carcinomas, especially in those of peripheral location (Dingemans and Mooi, 1986). We have demonstrated this alveolar trapping in three of our cases, which were widely present in two cases and limited to the periphery of the neoplasm in the last one. In the first two cases the tumor grew interstitially, concentrically narrowing the alveoli and displacing alveolar epithelium to the center of the lumina. In some areas the trapped alveoli were partially destroyed and only small groups or isolated alveolar cells were found inside the tumor, usually adjacent to alveolar septa. Tumor cells seem, therefore, able to ulcerate the alveolar lining and penetrate into the interstitium of the alveoli or incorporate the non-neoplastic alveolar epithelial cells into the tumor mass, resulting in an interstitial growth pattern similar to that found in the growing edge of

sarcomas in the lung. The cells do not seem to be substantially damaged or destroyed (Dingemans and Mooi 1986), surviving sometimes in very deeply situated areas of the tumor far away from the edge of the tumor. In this location the cells can differentiate and develop small neolumina (Alvarez Fernandez, 1982). It is remarkable that this phenomenon can occur in a tumor as aggressive as carcinoma with a rhabdoid phenotype, a finding not described before, in which a more destructive growth and a lesser possibility of normal cells survival could be expected. It could be hypothesized that tumor cells grow along the basal lamina because it is an area of tissular weakness inasmuch as the cells spread easily on this lamina and even extend small pseudopodic expansions through the basal lamina but without migrating through it (Dingemans and Mooi, 1986). The fact that in our cases in some areas the alveoli were partially destroyed or that even small groups of alveolar residual cells were found, is in favor of the progressive substitution of the preserved and trapped alveoli by tumoral cells, where in advanced tumors the capacity of invasion and destruction overrun the normal structures, as are in this case the trapped alveoli.

AntiTTF1 antibodies seem to be the most useful and simplest method to distinguish this pattern, as the tumor cells stain negatively in most cases, whereas the trapped alveoli are positive, especially in areas where the alveolar lumina are small or distorted and partially replaced by the tumor. Residual alveolar cells have been found by conventional histology, when the alveoli were still recognized (Alvarez-Fernández, 1982; Dingemans and Mooi, 1986; Paakko et al., 1990; Nakanishi et al., 1996; Funai et al., 2003; Kobayashi et al., 2006), by electron microscopy, enzymatic histochemistry and histoblood group inmunohistochemistry (Alvarez-Fernández, 1982; Dingemans and Mooi, 1986; Nakanishi et al., 1996) or with antibodies for apoprotein of the surfactant, specific for type II pneumocytes (Nakanishi et al., 1996). TTF1 had not been used before, and rendered similar results to those obtained using more complex and time-consuming techniques.

Funai et al. (2003) found alveolar lumina preserved only in the alveolar space-filling type of peripheral squamous cell carcinoma which showed non-aggressive histologic features and a growth from one alveolus to another through the pores of Cohn. Its prognostic significance has been studied only by Mochizuki et al. (2008) in their series of pleomorphic carcinoma of lung and they found that this feature is not a statistically significant factor for survival of the patients.

The interstitial growth pattern and the rhabdoid pseudomesenchymal morphology can simulate the interstitial septal growth of some sarcomas and could lead to a misinterpretation of the nature of the tumor in small or poorly preserved biopsies. Moreover, the presence of preserved alveoli inside of a solid tumor with a pseudobiphasic pattern (solid and luminal with pseudoglands) could also be mistaken for a neoplasm with a true biphasic pattern as an adenosquamous carcinoma. However, the benign morphology and immunohistochemical features of the cells lining the alveolar trapped lumina and the absence of mucinous material within these structures help to recognize this component as trapped alveoli instead of the malignant glands of the adenocarcinomatous areas present in the adenosquamous carcinoma.

In summary, we report seven new cases of lung carcinoma with a rhabdoid phenotype. This tumor variant is associated with a wider spectrum of histological subtypes than previously reported. However, it must be remarked the association with other high grade histological types as sarcomatoid, pleomorphic or micropapillary, and that most cases are diagnosed at advanced stages. Therefore further studies are needed to evaluate its prognostic significance and possibly to redefine the rhabdoid phenotype.

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