American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e932452
DOI: 10.12659/AJCR.932452

Received: 2021.03.29
Accepted: 2021.07.01
Available online: 2021.07.14
Published: 2021.08.25

Transition From Distinct Types of *KRAS* Mutation-Harboring Multifocal Lung Adenocarcinoma to Rhabdoid Tumor: A Longitudinal Follow-Up

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Kensuke Setoguchi*
ABCDEFG 1 Shigehisa Yanagi*
ADE 2 Toshihiro Gi
AE 1 Hironobu Tsubouchi
ABCDEF 1 Kazuko Uto
ABE 1 Takafumi Shigekusa
AE 1 Nobuhiro Matsumoto
AE 3 Yuichiro Sato
AE 1 Masamitsu Nakazato

1 Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki City, Miyazaki, Japan
2 Department of Pathology, Faculty of Medicine, University of Miyazaki, Miyazaki City, Miyazaki, Japan
3 Department of Diagnostic Pathology, University of Miyazaki Hospital, University of Miyazaki, Miyazaki City, Miyazaki, Japan

* Kensuke Setoguchi and Shigehisa Yanagi contributed equally to this work as first authors

Corresponding Author: Shigehisa Yanagi, e-mail: yanagi@med.miyazaki-u.ac.jp
Conflict of interest: None declared
Financial support: This work was supported by the Shinnihon Foundation of Advanced Medical Treatment Research (to S.Y.)

Patient: Female, 78-year-old
Final Diagnosis: Rhabdoid tumor of the lung
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Rhabdoid tumor (RT) of the lung is a rare and aggressive malignancy. The origin of and the mutation responsible for RT are entirely unknown. The distinction between RT associated with subtypes of lung cancer and SMARCA4-deficient thoracic sarcomas is also unknown.

Case Report: Three pulmonary subsolid nodules in the right S6, left S6, and left S8 were identified in a 78-year-old Japanese woman. At 3 and 9 months later, a chest CT showed unchanged sizes, but at 15 months the development of a 37-mm mass in the right S6 was observed. The patient's systemic condition deteriorated rapidly, and she died 1 month later. An autopsy revealed that the mass consisted of 90% RT and 10% lung adenocarcinoma. There were another 2 adenocarcinoma lesions in the left lung. *KRAS* mutation analyses revealed the same *KRAS* mutation (G12D) in the adenocarcinoma and RT components in the identical mass and metastatic RT, indicating that all of these components had the same clonality. A different *KRAS* mutation in each of the 3 adenocarcinoma lesions was detected (right S6: G12D, left S6: A59G, left S8: G12C), indicating that the multiple adenocarcinoma lesions were truly multifocal lung adenocarcinoma. The adenocarcinoma and RT components retained SMARCA4 expression.

Conclusions: This is the first evidence of RT originating from multifocal lung adenocarcinoma. *KRAS* mutation is thought to be responsible for the RT's emergence via the epithelial-mesenchymal transition. Patients with multiple subsolid nodules should be followed closely; aggressive surgical intervention should be considered given concerns about the evolution of this aggressive malignancy.

Keywords: KRAS Protein, Human • Rhabdoid Tumor • SMARCA2 Protein, Human

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932452

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Rhabdoid tumor (RT), a highly aggressive neoplasm, was first described in 1978 as a childhood-onset distinctive renal tumor [1]. Several cases of adult-onset RTs have been reported in the kidneys as well as extrarenal sites including the lungs [2,3]. In the 2004 World Health Organization (WHO) classification, large-cell carcinoma with rhabdoid phenotype (LCC-RP) was grouped as a variant type of large-cell carcinoma [4]. LCC-RP is defined as having malignant tumor cells comprised of ≥10% rhabdoid cells, which are characterized by abundant acidophilic cytoplasm, large nuclei, and conspicuous eosinophilic cytoplasmic globules [5]. LCC-RP is extremely rare, and it is an aggressive malignancy with a poor prognosis [5,6].

In the 2015 WHO classification, the rhabdoid phenotype was regarded as a cytologic feature rather than a specific histologic group, as it colocalizes with various histologic subtypes [7,8]. More recently, SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4)-deficient thoracic sarcomas (SMARCA4-DTSs) were proposed as a distinctive disease entity with rhabdoid morphology and highly aggressive malignancy [9]. To date, direct evidence of the cell lineage in which RTs arise from a specific subtype of lung cancer has not been obtained. The driver oncogene(s) responsible for the occurrence of RT in lung cancer are also not fully understood. Moreover, the distinction between RT associated with subtypes of lung cancer and SMARCA4-DTSs remains to be determined.

Here, we report a patient with RT arising from multifocal lung adenocarcinoma. The results of our longitudinal chest computed tomography (CT) and *KRAS* mutation analyses demonstrated that the patient's RT originated from one of the multifocal lung adenocarcinomas. An immunohistochemical study revealed that inactivation of SMARCA4 gene was unaffected in the patient. To the best of our knowledge, this is the first case report in which the emergence of RT within a multifocal lung adenocarcinoma lesion was captured during a sequential chest CT follow-up.

Case Report

A 78-year-old Japanese woman presented with a 1-month history of dyspnea on effort. She had never smoked and had no history of alcohol use or dust exposure. She had a 32-year history of systemic lupus erythematosus, and she had been continuously treated with oral prednisolone (4 mg/day) and mizoribine (50 mg/day). She had undergone radical surgery for ascending colon cancer 4 years before her presentation. The chest CT at presentation demonstrated 3 subsolid nodules in her lung fields: an 11-mm subsolid nodule in the superior (S6) segment of the right lower lobe, a 9-mm subsolid nodule in the superior (S6) segment of the left lower lobe, and an 8-mm subsolid nodule in the anteromedial (S8) segment of the left lower lobe (**Figure 1**).

A transbronchial biopsy was performed for the lesion in the right S6 segment, but no definite diagnosis was made. The patient was then followed-up by chest CT assessments, and the chest CT examinations conducted 3 and 9 months later showed that the nodules had remained unchanged in size. However, a chest CT at 15 months demonstrated the development of a 37-mm mass lesion in the right S6 segment. A CT-guided needle biopsy was performed for the mass lesion at 16 months. The pathology assessment of the needle-biopsied specimen revealed that the mass lesion was composed of carcinoma cells with rhabdoid features, characterized by large cells with eccentrically located nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and large intracytoplasmic inclusions. The tumor cells were negative for *EGFR* mutations and *ALK* gene rearrangement.

Immunohistochemistry results showed that the programmed death-1 ligand-1 tumor proportion score of the tissue sample was 50%. A chest CT examination revealed the rapid growth of the mass lesion (from 37 mm to 60 mm within 1 month) (**Figure 1**). The subsolid nodules in the left S6 and S8 segments were unchanged in size throughout the clinical course. At 17 months, the patient was hospitalized with fever, wet cough, bloody sputum, and appetite loss. Her systemic condition deteriorated rapidly, and her Eastern Cooperative Oncology Group performance status fell to 4. We therefore decided to manage her treatment as best supportive care. She died 1 month after being hospitalized.

The autopsy revealed that there was a 65-mm mass lesion in the right S6 segment with extensive hemorrhage and necrosis (**Figure 2A**). The mass consisted of 90% solid tumor with rhabdoid cells and 10% non-mucinous adenocarcinoma lesion with focal intracytoplasmic mucin (**Figure 2B-2D**). A continuum of changes from adenocarcinoma to the solid area with rhabdoid cells was observed, suggesting the process of epithelial-mesenchymal transition (EMT) (**Figure 2E**). The adenocarcinoma lesion was positive for cytokeratin (CK) AE1/AE3 (a pan-cytokeratin marker), CAM5.2 (a pan-cytokeratin marker), CK7, and CK20 (**Figure 3A, 3C, 3F, 3G**). Mucin 5AC (MUC5AC) immunopositivity was detected in a small part of the adenocarcinoma lesion (**Figure 3H**). The immunoreactivity for hepatocyte nuclear factor 4α (HNF4α) was scant (**Figure 3I**). Rhabdoid cells were positive for AE1/AE3, CAM5.2, and vimentin but negative for CK7, CK20, MUC5AC, and HNF4α (**Figure 3B, 3D, 3E**). Multiple metastatic foci of RT were observed in the pancreas, lungs, heart, gall bladder, and soft palate. There were another 2 adenocarcinoma lesions in the S6 and S8 segments of the

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

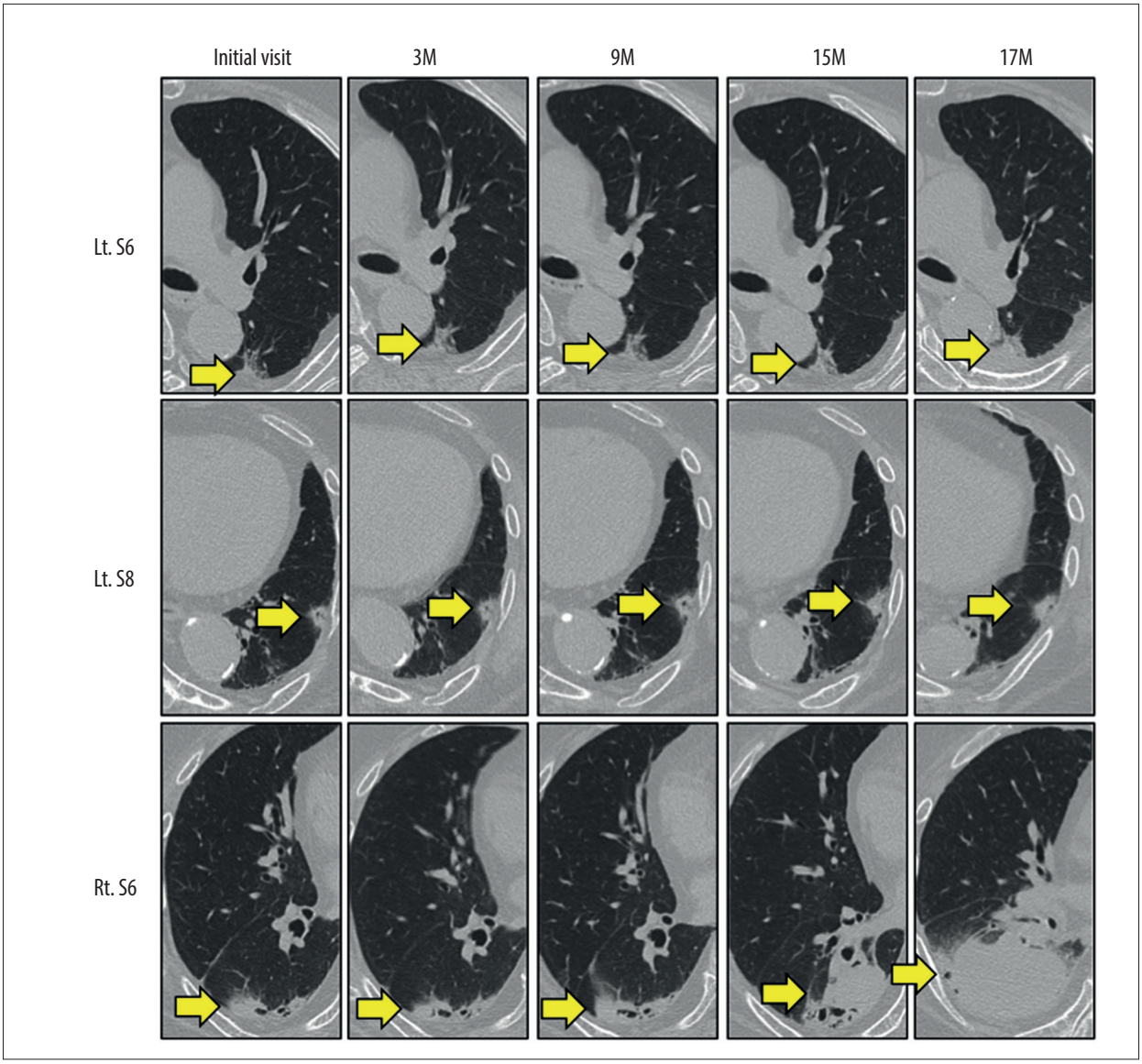

Figure 1. Chest CT findings in the longitudinal follow-up. A chest CT on the patient's initial visit demonstrated 3 subsolid nodules in the lung fields: a 9-mm subsolid nodule in the superior (S6) segment of the left lower lobe (**upper left panel**), an 8-mm subsolid nodule in the anteromedial (S8) segment of the left lower lobe (**middle left panel**), and an 11-mm subsolid nodule in the superior (S6) segment of the right lower lobe (**lower left panel**). The mass lesion in the right S6 segment had grown from 11 mm to 37 mm at 15 months. The mass in the right S6 segment grew from 37 mm to 60 mm within 1 month. The subsolid nodules in the left S6 and S8 segments were unchanged in size through the clinical course.

left lower lobe (**Figure 4A-4E**). There was no evidence of the recurrence of the preexisting colon cancer.

To investigate whether the adenocarcinomas and RT had the same origin, we analyzed *RAS* mutation in each tumor lesion by performing an amplification refractory mutation system/Scorpion PCR assay [10]. The study protocol was approved by the University of Miyazaki Research Ethics Committee (No. C-0040). Informed consent was obtained from the patient's family. Both tumor components (the adenocarcinoma lesion and the RT lesion) were microdissected from the right S6 specimen.

The *RAS* mutation analysis revealed the same *KRAS* mutation, G12D, in both the adenocarcinoma and the RT components in the right S6 mass lesion (**Figure 5**). The metastatic lesion of RT in the soft palate also had the same *KRAS* mutation (G12D). The adenocarcinoma lesions in the left S6 and left S8 segments had different *KRAS* mutations – A59G and G12C, respectively.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

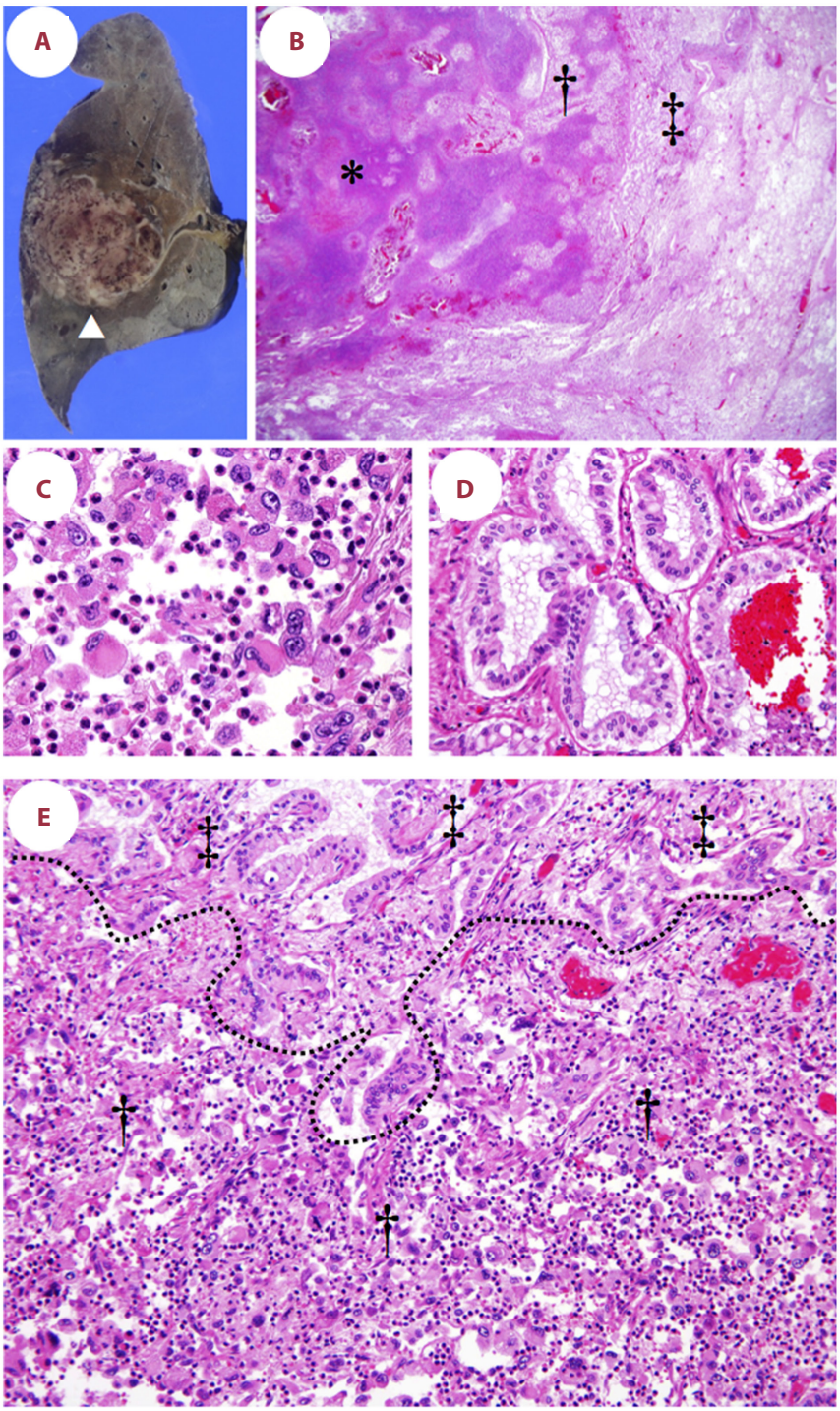

Figure 2. Autopsy findings of the right lower lobe of the lung. (**A**) Gross appearance. The tumor was well- to partly ill-demarcated and irregularly shaped with massive hemorrhage (*arrowhead*). (**B-E**) Histological examination of the right S6 mass specimens revealed an extensive necrotic area (* in **B**) with a component of the solid area with rhabdoid cells, characterized by large cells with eccentrically located nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and large paranuclear intracytoplasmic inclusions († in **B, C**). The tumor also had a component of non-mucinous adenocarcinoma with focal intracytoplasmic mucin (‡ in **B, D**). (**E**) A continuum of changes from adenocarcinoma (‡) to the solid area with rhabdoid cells (†). **B:** 15×; **C:** 400×; **D, E:** 200× magnification. Hematoxylin and eosin (H&E) stain.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

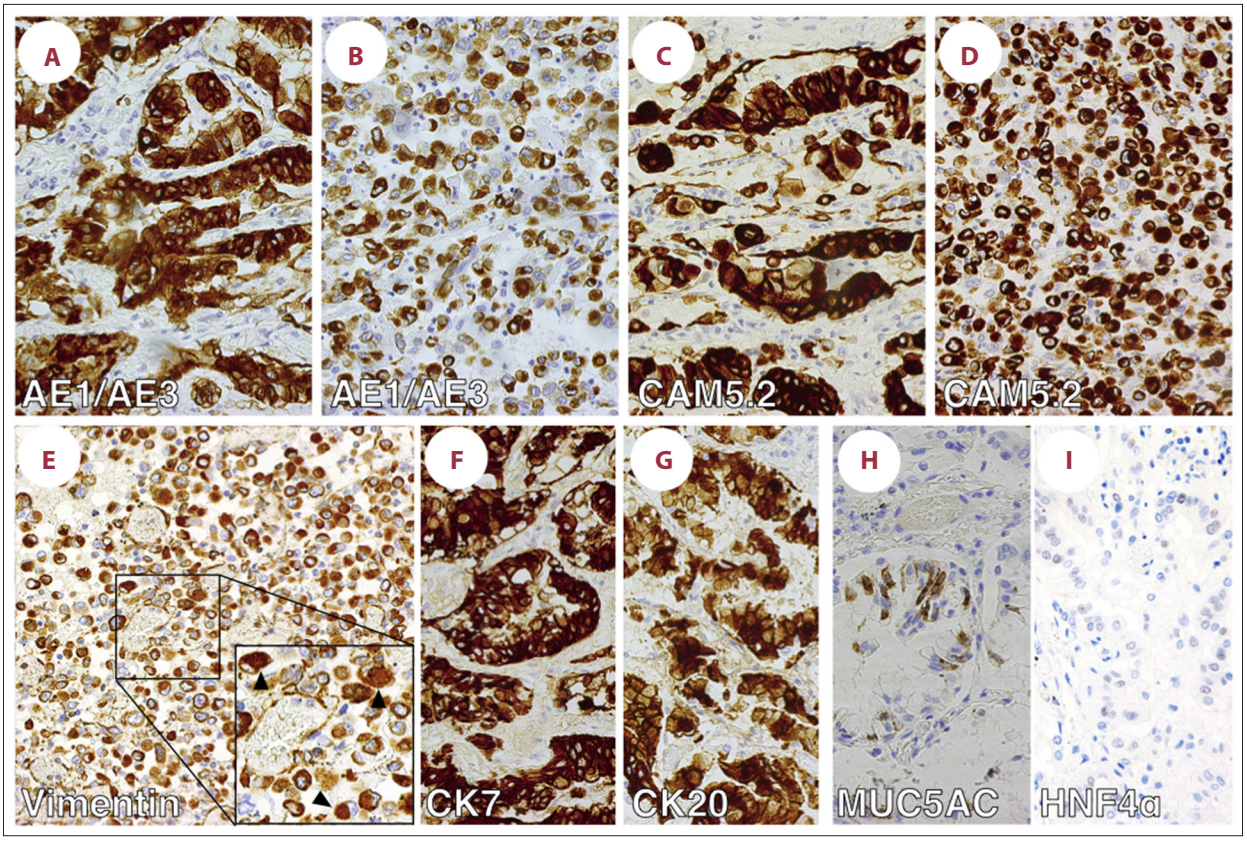

Figure 3. Immunohistochemical findings of the tumor in the right lobe of the lung. The adenocarcinoma component was positive for AE1/AE3 (**A**), CAM 5.2 (**C**), CK7 (**F**), and CK20 (**G**). Little immunopositivity for MUC5AC (**H**) and HNF4α (**I**) was observed in the adenocarcinoma lesion. The component of rhabdoid cells was positive for AE1/AE3 (**B**), CAM 5.2 (**D**), and vimentin (**E**). Paranuclear intracytoplasmic inclusions were strongly positive for vimentin in some of the rhabdoid cells (E, *arrowheads*). **A-I:** 200× magn.

We then investigated the involvement of *SMARCA4* gene deficiency in the emergence of the RT by evaluating the nuclear expression of SMARCA4 [9,11-14]. On immunohistochemistry, both the adenocarcinoma and the RT components in the right S6 mass lesion retained nuclear expression for SMARCA4 (BRG1; **Figure 6A-6C**), suggesting that *SMARCA4* gene was unaffected in our patient's case.

Discussion

Rhabdoid tumor of the lung is an extremely rare type of lung cancer characterized by a highly aggressive malignancy property. The origin of RT and its responsible driver oncogene remain unclear. This is the first case report identifying an RT that had originated from a multifocal adenocarcinoma in the lung. The longitudinal CT findings and the results of our *KRAS* mutational analyses suggest that the multifocal lung adenocarcinoma was the source of our patient's RT by activating a mutation in the *KRAS* gene as its driver oncogene. This patient's case strongly highlights the necessity for more careful attention during the follow-up of multifocal subsolid nodules in the lungs, in order to detect the occurrence of this highly aggressive malignancy.

Several case studies have reported RTs in the lung that co-localized with various subgroups of differentiated lung cancer. Based on our literature search, as of March 20, 2021, 54 cases of RT in the lung have been described in 22 published articles (**Table 1**) [5,6,15-34]. Among these cases, 50 case reports noted the associated tumor types: adenocarcinoma (30%, 15 of the 50 cases), large-cell carcinoma (28%, 14 cases), poorly or undifferentiated tumor (10%, 5 cases), sarcomatoid carcinoma (8%, 4 cases), large-cell neuroendocrine carcinoma (6%, 3 cases), squamous cell carcinoma (4%, 2 cases), small cell carcinoma (4%, 2 cases), invasive mucinous adenocarcinoma (IMA, 2%, one case), and more. This is the first case report to describe a patient with RT associated with multifocal lung adenocarcinoma.

Since some of the adenocarcinoma cells contained intracytoplasmic mucin in our patient's case, we initially considered IMA

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

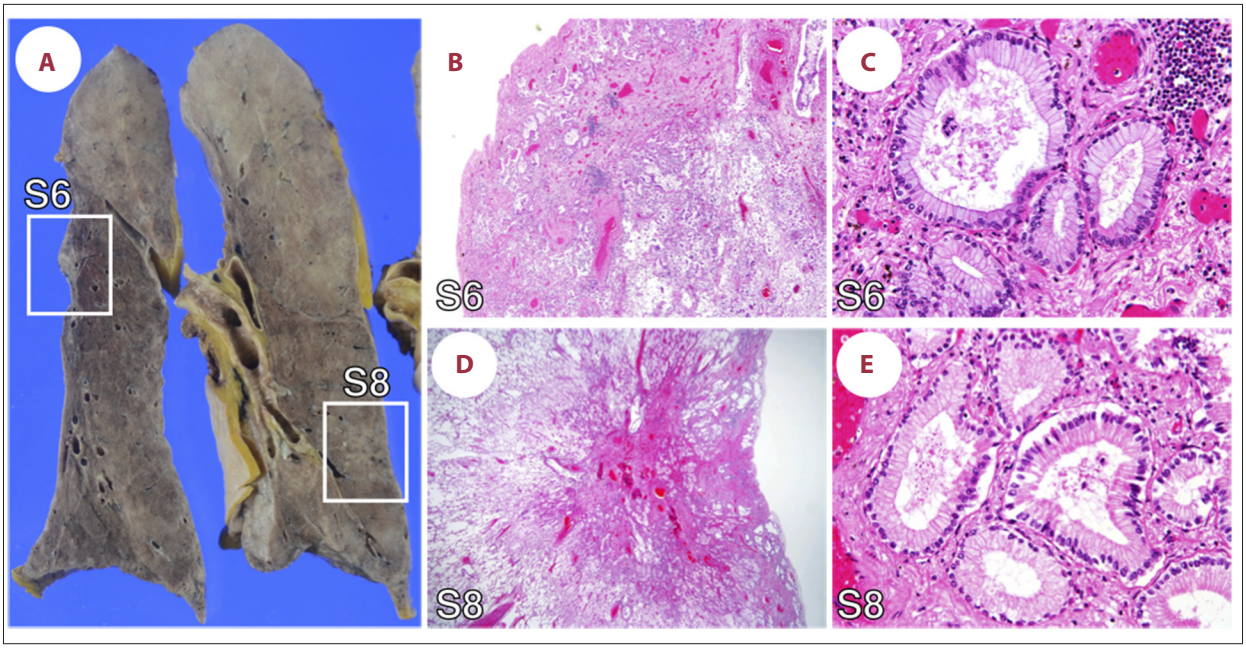

Figure 4. Autopsy findings of the left lower lobe of the lung. **A:** Gross appearance. The tumors located in the left S6 and left S8 segments are shown. Histological examination of the nodules in the left S6 (**B, C**) and left S8 (**D, E**) segments revealed adenocarcinoma lesion with focal intracytoplasmic mucin. **B:** 40×; **C, E:** 400×; **D:** 12.5× magn. H&E stain.

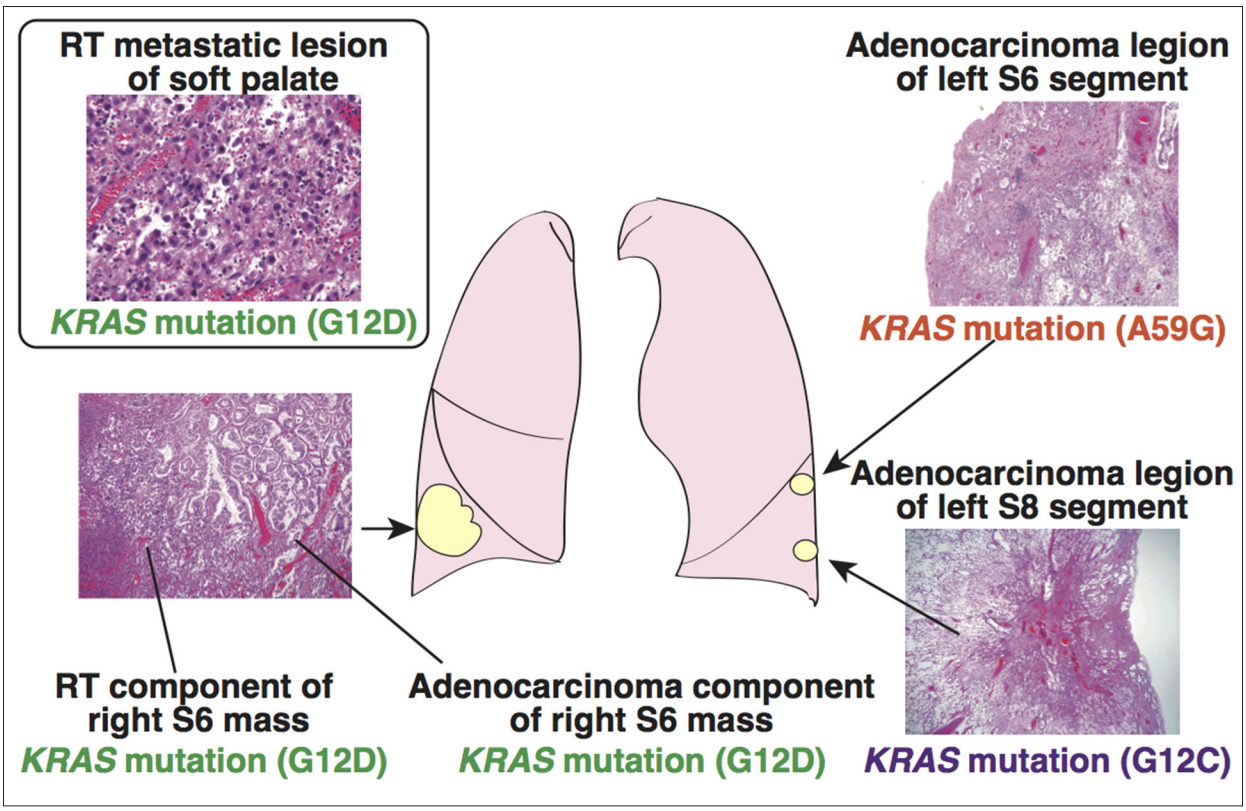

Figure 5. *KRAS* mutational analyses. The same *KRAS* mutation (G12D) was detected in both components of the rhabdoid tumor and the adenocarcinoma in the tumor of the right S6 segment as well as a metastatic rhabdoid tumor in the soft palate. The adenocarcinomas in the left S6 and left S8 segments possessed different types of *KRAS* mutation, i.e., A59G and G12C, respectively.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

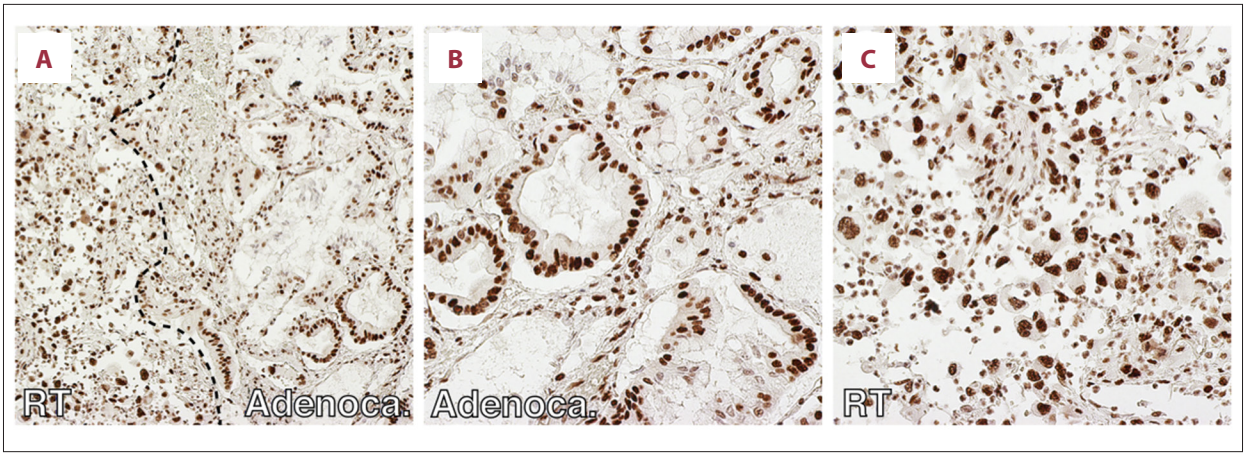

Figure 6. Immunohistochemical findings of SMARCA4 (BRG1, **A-C**). Both adenocarcinoma cells (**B**) and rhabdoid tumor cells (**C**) retained nuclear expression of SMARCA4. **A:** 100×; **B, C:** 200× magn.

as a differential diagnosis of non-mucinous lung adenocarcinoma. However, several of the findings were different from the essential and desirable diagnostic criteria of IMA described in the most recent published WHO classification of thoracic tumors [35]. First, almost none of tumor cells in our patient's case had abundant apical columnar cells with small basally oriented nuclei. Second, the immunopositivity of MUC5AC and HNF4α, which are markers of IMA, was scant in the present case. A recent study with a comprehensive genomic analysis demonstrated the clonal relationship of spatially separate IMA lesions: among 24 patients with 2 separate IMAs, tumors from all but 1 patient shared the same driver mutations [36]. In contrast, in the present study, each adenocarcinoma lesion possessed a different type of KRAS mutation. We thus concluded that all 3 of these adenocarcinomas were not IMAs, but rather were non-mucinous adenocarcinomas with intracytoplasmic mucin.

In our patient's case, 4 findings indicated that the multifocal adenocarcinoma underwent a transition to RT. First, the histology showed the presence of the continuum of changes from adenocarcinoma to the solid area with rhabdoid cells, suggesting the EMT process. Second, the immunohistochemical study exhibited continuous changes of epithelial- and mesenchymal-marker expression between the adenocarcinoma and RT areas. Third, the *KRAS* mutation analyses revealed the same *KRAS* mutation (G12D) in one of the adenocarcinoma components and the RT component in the identical mass lesion and metastatic RT lesion, indicating that all 3 of these components had the same clonality. The different *KRAS* mutations in each of the 3 adenocarcinoma lesions (G12D in the adenocarcinoma lesion in right S6, A59G in the adenocarcinoma lesion in left S6, and G12C in the adenocarcinoma lesion in left S8) also clearly indicated that the multiple adenocarcinomas in our patient were a bona fide multifocal lung adenocarcinoma. Fourth, the RT arose within one of the multifocal adenocarcinoma lesions during the chest CT follow-up for multiple subsolid nodules. Importantly, all of the reported RT cases in the lung are RTs that were observed at the first presentation. In contrast, at our patient's initial visit, there were only multiple subsolid nodules (corresponding to adenocarcinoma lesions) and no mass shadow (corresponding to an RT lesion). After the mass shadow appeared, it grew rapidly, reflecting the aggressive phenotype of RT. The emergence and rapid development of RT within the adenocarcinoma lesion were captured in the longitudinal chest CT follow-up. In this respect, our report provides strong evidence that a multifocal adenocarcinoma can actually undergo a transition to RT.

The EMT plays pivotal roles in cancer biology including tumor growth, invasion, dissemination, and metastasis [37]. Since EMT-suggestive findings were observed in the RT specimen in the lung in the present and previous cases [26,31], the EMT might be key to the dedifferentiation of parental cancer cells to rhabdoid cells in the lung. Regarding the mutation responsible for RT evolution, Dettmer et al showed the existence of the same *EGFR* activating mutation – exon 19 deletion – in both the adenocarcinoma part and the RT part within a single tumor lesion [31]. This finding suggests that these 2 tumor components have the same origin. However, since the *EGFR* deletion mutation does not induce the EMT by itself [38], it is unlikely that this *EGFR* mutation directly induces RT emergence. In our patient's case, we identified the same *KRAS* mutation, G12D, in both the adenocarcinoma and RT components. We also observed that *EGFR* gene or *ALK* gene was the wildtype in the RT lesion in the present case. Because G12D is an activating oncogenic mutation of *KRAS*, which in turn facilitates a transcriptional program involved in EMT [39,40], we believe that the RT emergence from the adenocarcinoma reported herein was caused by *KRAS* G12D mutation via the EMT.

In 2015, Le Loarer and colleagues demonstrated that *SMARCA4*, which encodes an ATPase subunit of BAF chromatin-remodeling

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1. Summary of 54 lung carcinoma with rhabdoid tumor cases in published articles.

No.	Author, Year	Age	Sex	Symptoms	Smoking history	Tumor diameter (cm)	Metastatic organ
1	Cavazza et al 1996	54	F	Hemoptysis	Yes	NA	LN
2		36	M	Chest pain	NA	NA	None
3		47	M	Hemoptysis	Yes	NA	None
4		71	F	NA	NA	NA	LN, PeCa
5		71	M	NA	NA	NA	None
6		25	F	Bazex's syndrome	No	NA	Lung, LN
7	Rubenchik et al 1996	74	M	None	Yes	3.5	None
8	Chetty et al 1997	68	M	Cough, hemoptysis	No	3	LN
9		62	F	Cough, hemoptysis, wheezing	Yes	11	None
10		40	M	Cough, chest pain, dyspnea	Yes	6	NA
11	Chetty 2000	50	F	Cough, dyspnea	Yes	17	LN
12		53	M	Cough, hemoptysis	Yes	12	None
13	Miyagi et al 2000	51	M	Hemoptysis	Yes	4	LN
14		72	M	Cough	No	5.6	LN
15		50	F	Fatigue	No	3	None
16	Shimazaki et al 2001	69	M	None	NA	4.5	None
17		66	M	Hemoptysis	NA	6	None
18		82	M	Chest pain, cough, dyspnea	Yes	11	None
19		47	F	Hemoptysis, cough	Yes	8.5	LN
20	Attems et al 2001	69	F	Chest pain	Yes	2	AG, skin, duodenum
21	Kaneko et al 2002	59	M	None	Yes	4.5	AG
22	Hiroshima et al 2003	70	F	None	NA	1.5	None
23	Tamboli et al 2004	57	M	Respiratory	Yes	23	NA
24		57	F	Hemoptysis	Yes	4	Brain, jejunum
25		54	M	Hemoptysis	Yes	4	Liver, bone, LN
26		48	F	Hoarseness	Yes	5.1	Lung, LN
27		54	M	Hemoptysis, GI bleeding	NA	10	Soft tissue, bowel, LN
28		70	M	Knot in the chest wall	Yes	NA	Bone, chest wall
29		61	M	Hemoptysis	Yes	4.7	LN, bone
30		59	F	Cough	Yes	NA	Brain, bone, lung, LN
31		34	M	Hemoptysis	NA	2	Lung
32		65	M	Mass in the chest wall	NA	NA	Chest wall
33		59	F	Hemoptysis	Yes	3	LN

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Summary of 54 lung carcinoma with rhabdoid tumor cases in published articles.

No.	Author, Year	Age	Sex	Symptoms	Smoking history	Tumor diameter (cm)	Metastatic organ
34	Yilmazbayhan et al 2005	55	M	Chest pain, cough, hemoptysis	Yes	3.5	Liver, LN spleen
35	Falconieri et al 2005	50	M	Chest pain	NA	8	None
36		58	F	Cough, chest pain, dyspnea	NA	3	None
37		56	M	Chest pain, weight loss	NA	4	None
38		63	M	Couth, chest pain, weight loss	NA	4.8	Brain
39	Goto et al 2006	37	M	Cough, hemoptysis	Yes	5	LN, intestine, AG
40	Song et al 2007	59	M	Hemoptysis, chest discomfort	NA	10	AG
41	Saini et al 2009	36	F	Hemoptysis	No	6	None
42	Izquierdo-Garcia 2010	59	M	None	Yes	3.5	AG
43		52	M	Hemoptysis	Yes	8	Lung
44		59	F	Chest pain	Yes	8	Lung, LN, liver, bone
45		64	M	None	Yes	3	AG, LN, bone
46		39	M	Cough, chest pain, hemoptysis	Yes	9	None
47		68	M	None	Yes	1.5	Lung, bone
48		76	F	None	No	4	None
49	Otera 2010	63	M	Abdominal pain	Yes	9.5	LN, small intestine
50	Attia 2011	36	M	Chest pain, dyspnea, cough, weight loss	No	NA	LN
51	Dettmer 2012	64	M	Cough, hemoptysis	No	6.1	LN
52	Kim 2014	48	M	Hemoptysis	Yes	20	None
53	Bahadur 2015	65	F	Lump in the axilla	No	9	LN
54	Zysman 2016	26	M	Hemoptysis	Yes	NA	NA

No.	Author, Year	Rhabdoid cells (%)	Associated tumor type	Driver mutation	Follow-up (months)	Vital status	Ref.
1	Cavazza et al 1996	90	LCC	NA	6	Alive	[5]
2		>10	Sarcoma	NA	4	Alive	[5]
3		>10	Ad	NA	4	Dead	[5]
4		10	Ad	NA	2	Alive	[5]
5		>10	LCC	NA	5	Alive	[5]
6		10	LCC	NA	NA	NA	[5]
7	Rubenchik et al 1996	Most	NA	NA	24	Alive	[15]

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Summary of 54 lung carcinoma with rhabdoid tumor cases in published articles.

No.	Author, Year	Rhabdoid cells (%)	Associated tumor type	Driver mutation	Follow-up (months)	Vital status	Ref.
8	Chetty et al 1997	>10	Ad	NA	6	Dead	[16]
9		25	LCNEC	NA	3	Dead	[16]
10		>10	Ad	NA	6	NA	[16]
11	Chetty 2000	15	LCNEC, SCC	NA	6	Dead	[17]
12		10	LCNEC, SCC, SqCC	NA	12	Dead	[17]
13	Miyagi et al 2000	70	Ad	NA	36	Dead	[18]
14		90	Ad	NA	4	Dead	[18]
15		50	Ad	NA	41	Alive	[18]
16	Shimazaki et al 2001	18.2	PDUT	NA	1.5	Dead	[6]
17		15.5	PDUT	NA	0.6	Dead	[6]
18		15	PDUT	NA	1	Dead	[6]
19		60	PDUT	NA	10	Dead	[6]
20	Attems et al 2001	NA	PMAC	NA	3	Dead	[19]
21	Kaneko et al 2002	90	LCC	NA	63	Alive	[20]
22	Hiroshima et al 2003	Most	LCC	NA	72	Alive	[21]
23	Tamboli et al 2004	25	SarC	NA	NA	LFU	[22]
24		90	LCC	NA	11	Dead	[22]
25		15	LCC	NA	4	Dead	[22]
26		10	Ad	NA	19	Dead	[22]
27		90	LCC	NA	5	Dead	[22]
28		90	Ad	NA	10	Dead	[22]
29		30	SarC	NA	15	Dead	[22]
30		50	Ad	NA	3	Dead	[22]
31		60	SarC	NA	3	Dead	[22]
32		75	SarC	NA	NA	LFU	[22]
33		20	Ad	NA	20	Alive	[22]
34	Yilmazbayhan et al 2005	100	LCC	NA	2	Dead	[23]
35	Falconieri et al 2005	100	ERC	NA	NA	Alive	[24]
36		100	ERC	NA	NA	Alive	[24]
37		100	ERC	NA	NA	LFU	[24]
38		100	ERC	NA	NA	Dead	[24]
39	Goto et al 2006	Most	LCC	NA	6	Dead	[25]
40	Song et al 2007	30	IMA	NA	NA	Alive	[26]
41	Saini et al 2009	Most	LCC	NA	57	Alive	[27]

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Summary of 54 lung carcinoma with rhabdoid tumor cases in published articles.

No.	Author, Year	Rhabdoid cells (%)	Associated tumor type	Driver mutation	Follow-up (months)	Vital status	Ref.
42	Izquierdo-Garcia 2010	30	Ad	NA	15	Dead	[28]
43		80	Pleomorphic	NA	6	Dead	[28]
44		50	Ad	NA	2	Dead	[28]
45		10	SqCC	NA	31	Dead	[28]
46		80	LCC	NA	123	Alive	[28]
47		10	LCC	NA	23	Dead	[28]
48		40	Ad	NA	6	Dead	[28]
49	Otera 2010	80	PDUT		1	Dead	[29]
50	Attia 2011	NA	NA	NA	NA	NA	[30]
51	Dettmer 2012	90	Ad	EGFR exon19 deletion	8	Alive	[31]
52	Kim 2014	Most	NA	NA	NA	Alive	[32]
53	Bahadur 2015	10	LCC	NA	NA	Alive	[33]
54	Zysman 2016	NA	NA	NA	3	Dead	[34]

Ad – adenocarcinoma; AG – adrenal gland; AIS – adenocarcinoma in situ; EGFR – epithelial growth factor receptor; ERC – exclusive rhabdoid carcinoma; IMA – invasive mucinous adenocarcinoma; LCC – large-cell carcinoma; LCNEC – large-cell neuroendocrine carcinoma; LN – lymph node; NA – not available; PDUT – poorly differentiated or undifferentiated tumor; Peric – pericardial; PMAC – pseudomesotheliomatous adenocarcinoma; SarC – sarcomatoid carcinoma; SCC – small-cell carcinoma; SqCC – squamous cell carcinoma.

complexes, is mutationally inactivated in thoracic undifferentiated malignancies with rhabdoid morphology and aggressive malignancy [9]. They designated this new type of thoracic malignancy 'SMARCA4-DTS.' Several research groups then reported cases of SMARCA4-DTSs located in the lung [11-14,41]. We here examined the involvement of *SMARCA4* deficiency in the development of RT in our patient, and we observed the retention of nuclear immunoreactivity of SMARCA4 in both the adenocarcinoma and RT lesions. Since all of the reported SMARCA4-DTSs cases demonstrated diminished SMARCA4 expression [11-14,41], we speculated that the *SMARCA4* gene in our patient was unaffected. Taking the past and present findings together, we believe that RT associated with subtypes of lung cancer and SMARCA4-DTSs, which are clinically and histologically indistinguishable rhabdoid tumors, are distinct disease entities and have different cell lineages. The fact that all of the SMARCA4-DTSs in the lung in the reported cases demonstrated the absence of a well-differentiated component such as glandular formation and keratinization [11-14,41,42] supports this idea. In addition to the pathogenic understanding, being able to distinguish SMARCA4-DTSs and RT associated with subtypes of lung cancer will be vital for making decisions about treatment, as each malignancy's respective molecular-targeted therapy could be developed [43,44].

Another important feature of our patient's case was the rapid growth of the mass during the CT follow-up for the management of the multiple subsolid nodules of the lung. The 2017 Fleischner Society Guidelines recommend that incidental pulmonary nodules be managed as follows: in patients with multiple subsolid lesions ≥6 mm, a short-term follow-up CT at 3-6 months should be considered [45]. Our patient's case emphasizes the necessity of considering aggressive surgical intervention (eg, multiple limited resections) in patients with multiple subsolid lesions in order to terminate the evolution of the RT.

Conclusions

We present the first case of a rhabdoid tumor arising from multifocal lung adenocarcinoma. *KRAS* mutation is considered to be responsible for the RT emergence in this patient, via the EMT. We propose that RT associated with subtypes of lung cancer and SMARCA4-DTSs are distinct disease entities. This report indicates that careful management and more aggressive surgical intervention should be considered in the management of multiple subsolid lesions, given concerns about the evolution of this aggressive tumor.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Acknowledgements

We thank Sumie Tajiri (University of Miyazaki) for her technical support.

Department and Institution Where Work Was Done

Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki City, Miyazaki, Japan.

Conflicts of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms tumors: Results from the First National Wilms' Tumor Study. Cancer. 1978;41:1937-48
2. Parham DM, Weeks DA, Beckwith JB. The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. Am J Sur Pathol. 1994;18:1010-29
3. Wick MR, Ritter JH, Dehner LP. Malignant rhabdoid tumors: A clinicopathologic review and conceptual discussion. Semin Diagn Pathol. 1995;12:233-48
4. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC. Pathology and genetics: Tumours of the lung, pleura, thymus and heart, IARC, Lyon, 2004
5. Cavazza A, Colby TV, Tsokos M, et al. Lung tumors with a rhabdoid phenotype. Am J Clin Pathol. 1996;105:182-88
6. Shimazaki H, Aida S, Sato M, et al. Lung carcinoma with rhabdoid cells: A clinicopathological study and survival analysis of 14 cases. Histopathology. 2001;38:425-34
7. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of tumours of the lung, pleura, thymus and heart, Lyon: International Agency for Research on Cancer, 2015
8. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10:1243-60
9. Le Loarer F, Watson S, Pierron G, et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet. 2015;47:1200-5
10. Nordgård O, Oltedal S, Janssen EA, et al. Comparison of a PNA clamp PCR and an ARMS/Scorpion PCR assay for the detection of K-ras mutations. Diagn Mol Pathol. 2012;21:9-13
11. Perret R, Chalabreysse L, Watson S, et al. SMARCA4-deficient thoracic sarcomas: Clinicopathologic study of 30 cases with an emphasis on their nosology and differential diagnoses. Am J Surg Pathol. 2019;43:455-6.
12. Rekhtman N, Montecalvo J, Chang JC, et al. SMARCA4-deficient thoracic sarcomatoid tumors represent primarily smoking-related undifferentiated carcinomas rather than primary thoracic sarcomas. J Thorac Oncol 2020;15:231-47
13. Sauter JL, Graham RP, Larsen BT, et al. SMARCA4-deficient thoracic sarcoma: A distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior. Mod Pathol. 2017;30:1422-32
14. Yoshida A. Kobayashi E, Kubo T et al. Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Mod Pathol. 2017;30:797-809
15. Rubenchik I., Dardick I, Auger M. Cytopathology and ultrastructure of primary rhabdoid tumor of lung. Ultrastruct Pathol. 1996;20:355-60
16. Chetty R, Bhana B, Batitang S, Govender D. Lung carcinomas composed of rhabdoid cells. Eur J Surg Oncol. 1997;23:432-34
17. Chetty R. Combined large cell neuroendocrine, small cell and squamous carcinomas of the lung with rhabdoid cells. Pathology. 2000;32:209-12
18. Miyagi J, Tsuhako K, Kinjo T, et al. Rhabdoid tumour of the lung is a dedifferentiated phenotype of pulmonary adenocarcinoma. Histopatology. 2000;37:37-44
19. Attems JH, Lintner F. Pseudomesotheliomatous adenocarcinoma of the lung with rhabdoid features. Pathol Res Pract. 2001;197:841-46
20. Kaneko T, Honda T, Fukushima M, et al. Large cell carcinoma of the lung with a rhabdoid phenotype. Pathol Int. 2002;52:643-47
21. Hiroshima K, Shibuya K, Shimamura F, et al. Pulmonary large cell carcinoma with rhabdoid phenotype. Ultrstruct Pathol. 2003;27:55-59
22. Tamboli P, Toprani TH, Amin MB et al. Carcinoma of lung with rhabdoid features. Hum Pathol 2004;35:8-13
23. Yilmazbayhan D, Ates LE, Dilege S, et al. Pulmonary large cell carcinoma with rhabdoid phenotype. Ann Diagn Pathol. 2005;9:223-26
24. Falconieri G, Moran CA, Pizzolitto S, et al. Intrathoracic rhabdoid carcinoma: A clinicopathological, immunohistochemical, and ultrastructural study of 6 cases. Ann Diagnos Pathol. 2005;9:279-83
25. Goto H, Ito M, Yamaguchi N, et al. [A case of large cell carcinoma of the lung with rhabdoid phenotype]. Nihon Kokyuki Gakkai Zasshi. 2006;44:325-29 [in Japanese]
26. Song DE, Jang SJ, Black J, Ro JY. Mucinous bronchioloalveolar carcinoma of lung with a rhabdoid component – report of a case and review of the literature. Histopathology. 2007;51:427-30
27. Saini G, Kumar M, Julka PK, et al. Rhabdoid variant of lung cancer: Clinicopathological details of a case and a review of literature. J Cancer Res Ther. 2009;5:54-57
28. Izquierdo-Garcia FM, Moreno-Mata N, Herranz-Aladro ML, et al. Lung carcinoma with rhabdoid component a series of seven cases associated with uncommon types of non-small cell lung carcinomas and alveolar entrapment. Histol Histopathol. 2010;25:1287-95
29. Otera H, Ikeda F, Nakagawa S, et al. Intussusception of small intestine due to metastasis of large cell carcinoma of the lung with a rhabdoid phenotype. Eur Respir Rev. 2010;117:248-52
30. Attia A, Suleman M, Mosleh H. Malignant rhabdoid tumor of the lung in the young adult: A case report. Case Rep Pulmonol. 2011;2011:332584
31. Dettmer M, Hench J, Pang B, et al. Rhabdoid large cell carcinoma of lung, with illustrative immunohistochemical and molecular findings. Appl Immunohistochem Mol Morphol. 2012;20:208-13
32. Kim MW, Rew SJ, Eun SJ, et al. A case of lung carcinoma with rhabdoid phenotype mimicking an aspergilloma in patient with recurrent hemoptysis. Tuberc Respir Dis. 2014;77:38-41
33. Bahadur S, Pujani M, Jetley S, et al. Large cell lung carcinoma with rhabdoid phenotype: Report of a rare entity presenting with chest wall involvement. J Cancer Res Ther. 2015;11:657
34. Zysman M, Clement-Duchene C, Bastien C, et al. Malignant rhabdoid tumor of the lung. Rev Mal Respir. 2016;33:808-11
35. WHO Classification of Tumours Editorial Board. Thoracic Tumours WHO Classification of Tumours, 5th Edition, Volume 5, 2021
36. Yang SR, Chang JC, Leduc C, Tan KS, et al. Invasive mucinous adenocarcinomas with spatially separate lung lesions: Analysis of clonal relationship by comparative molecular profiling. J Thorac Oncol. 2021;16:1188-99
37. Brabletz T, Kalluri R, Nieto MA, Weinberg RA. EMT in cancer. Nat Rev Cancer. 2018;18:128-34
38. Suda K, Tomizawa K, Fujii M, et al. Epithelial to mesenchymal transition in an epidermal growth factor receptor-mutant lung cancer cell line with acquired resistance to erlotinib. J Thorac Oncol 2011;6:1152-61
39. Arner EN, Du W, Brekken RA. Behind the wheels of epithelial plasticity in KRAS-driven cancers. Front Oncol. 2019;9:1049
40. Shao DD, Xue W, Krall EB, et al. KRAS and YAP1 converge to regulate EMT and tumor survival. Cell. 2014;158:171-84

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

41. Stewart BD, Kaye F, Machuca T, et al. SMARCA4-deficient thoracic sarcoma: A case report and review of literature. Int J Surg Pathol. 2020;28:102-8
42. Agaimy A, Fuchs F, Moskalev EA, et al. SMARCA4-deficient pulmonary adenocarcinoma: Clinicopathological, immunohistochemical, and molecular characteristics of a novel aggressive neoplasm with a consistent TTF1neg/CK7pos/HepPar-1pos immunophenotype. Virchows Arch. 2017;471:599-609
43. Drilon A, Schoenfeld AJ, Arbour KC, et al. Exceptional responders with invasive mucinous adenocarcinomas: A phase 2 trial of bortezomib in patients with KRAS G12D-mutant lung cancers. Cold Spring Harb Mol Case Stud. 2019;5:a003665
44. Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: A first-in-human, open-label, phase 1 study. Lancet Oncol. 2018;19:649-59
45. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT Images: from the Fleischner Society 2017. Radiology. 2017;284:228-43

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]