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Original contribution

Clinicopathologic study of deciduoid mesothelioma using SMARCB1/INI1 immunohistochemistry and fluorescence in situ hybridization ☆,☆☆,★

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Summary Deciduoid mesothelioma is a rare variant of epithelioid mesothelioma. Malignant rhabdoid tumors, renal medullary carcinoma, and some synovial sarcomas show a loss of SMARCB1/INI1 protein, a member of the SWI/SNF chromatin-remodeling complex. All of those tumors are known to have rhabdoid cells. Some mesothelioma cases, such as those of the deciduoid type, have also been reported to possess such rhabdoid features. Since this topic has not been studied in malignant mesothelioma, we analyzed the immunohistochemical expression of SMARCB1/INI1 in malignant mesotheliomas [45 epithelioid type (including 9 deciduoid type), 12 biphasic type, and 17 sarcomatoid type]. We employed (a) SMARCB1/INI1 immunohistochemistry, using an antibody to the *INI1* gene product and (b) Fisher exact test, logistic regression analysis, the Kaplan-Meier method, and the Wilcoxon test for survival analysis for prognostic factor evaluation (SAS 9.4; SAS Institute, Cary, NC). The results showed that 17 of 74 (23%) malignant mesothelioma cases (epithelioid: 24%; biphasic; 8%; sarcomatoid; 29%) had reduced SMARCB1/INI1 expression. Reduced SMARCB1/INI1 expression appeared to be more frequent in the deciduoid type (67%), of which there were admittedly only a few cases, than in either the epithelioid type (14%) or biphasic type (8%), whether or not rhabdoid cells were present, but not different between the deciduoid and sarcomatoid types. However, there was no statistically significant difference in prognosis between malignant mesotheliomas with reduced versus preserved SMARCB1/INI1 protein expression. The results suggest that in differential diagnosis, cases with reduced SMARCB1/INI1 protein expression should not be excluded from a diagnosis of malignant mesothelioma.

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1. Introduction

Epithelioid mesothelioma can be subdivided into solid, tubulopapillary, trabecular, micropapillary, adenomatoid, clear cell, signet ring, transitional, deciduoid, small, pleomorphic, lymphohistiocytoid, and myxoid types, according to the 4th edition WHO Tumor Classification [1]. Deciduoid mesothelioma is a rare variant of epithelioid mesothelioma that was initially reported to occur in the peritoneum of young females without a history of asbestos exposure [2,3]. Since then, this type of mesothelioma has been reported to occur in the pleura of men and women with asbestos exposure [4]. This type of mesothelioma sometimes exhibits rhabdoid features that are characterized by discohesive cells containing abundant cytoplasm and large eccentric nuclei with prominent nucleoli [4,5].

Table 1 SMARCB1/INI1protein expression in malignant mesothelioma

INI1	Deciduoid	Epithelioid	Biphasic	Sarcomatoid
Stain				
Preserved	3	31	11	12
Reduced	6	5	1	5
Fisher Exact test		0.0033	0.0158	0.1034

SMARCB1/INI1 is a member of the SWI/SNF multisubunit chromatin-remodeling complex located on the long arm of chromosome 22 (22q11.2) [6,7].

Malignant rhabdoid tumors, renal medullary carcinomas, epithelioid sarcomas, epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcomas, and some synovial sarcomas show a loss of SMARCB1/INI1 protein expression in tumor cells, and all of these tumors are known to have rhabdoid cells [8-13]. However, the literature contains no detailed study on this topic in malignant mesothelioma, only a single case report [14]. We analyzed the immunohistochemical expression of SMARCB1/INI1 in malignant mesotheliomas. In addition, we performed FISH analysis for homozygous and heterozygous deletion. Finally, Fisher exact test, logistic regression analysis, the Kaplan-Meier method, and the Wilcoxon test for survival analysis were employed for prognostic factor evaluation (SAS 9.4; SAS Institute, Cary, NC).

2. Materials and methods

2.1. Patients and tissue samples

Malignant mesotheliomas [45 epithelioid type (including 9 deciduoid type), 12 biphasic type, and 17 sarcomatoid type]

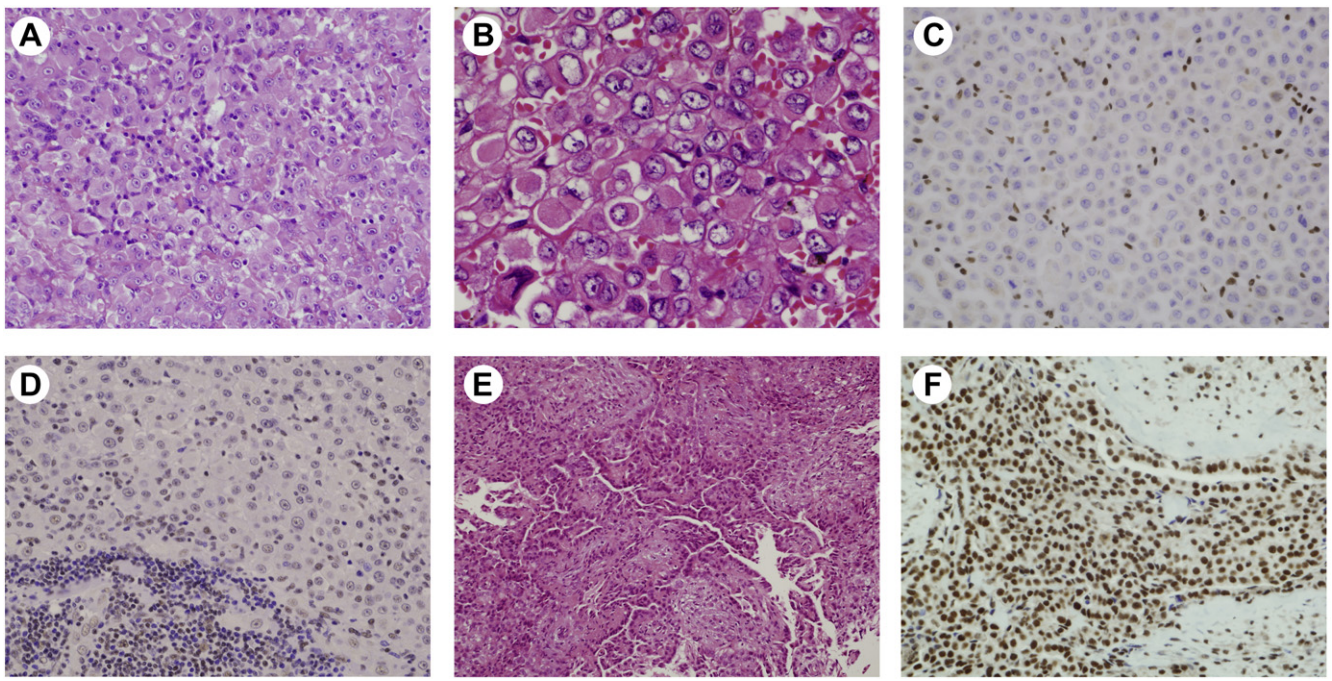

Figure 1 Histology and SMARCB1/INI1 immunohistochemistry of malignant mesothelioma. A, Deciduoid mesothelioma (75-year-old male, peritoneum). B, Deciduoid mesothelioma with rhabdoid feature (23-year-old female, peritoneum). C, Tumor cells showing complete loss of expression of SMARCB1/INI1 protein compared with the positive control, which included infiltrating lymphocytes (23-year-old female, peritoneum). D, Tumor cells showing reduced expression of SMARCB1/INI1 protein compared with the positive control including lymphocytes and histiocytes (75-year-old male, peritoneum). E, Malignant epithelioid mesothelioma, tubulopapillary type (79-year-old male, pleura). F, Tumor cells showing preserved SMARCB1/INI1 expression (79-year-old male, pleura).

Table 2 Relationship between SMARCB1expression and BAP-1 in malignant mesothelioma

	SMARCB1		
BAP-1	Reduced	+	Total
−	0	10	10
+	7	5	12
Total	7	15	22

P = .0053.

were collected in our laboratory at the National Defense Medical College, and at Oita Prefectural Hospital, Kochi Medical School Hospital, and Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan. Formalin-fixed paraffin-embedded neoplastic tissue blocks were available for all cases, together with clinical information. All procedures were performed with written informed consent and the study was approved by the institutional review board of the Toda Central Chuo Hospital (no.0366) and the National Defense Medical College (no.568) [15].

2.2. Immunohistochemistry

The labeled streptavidin biotinylated method (Ventana, AZ) was applied to deparaffinized sections of mesotheliomas. The primary mouse monoclonal antibody was BAF47, an antibody to the *INI-1* gene product (clone 25; 1:50; 32 min; Japan BD Transduction Laboratories, Fukushima, Japan). Non-tumor tissues, including entrapped normal tissue, such as inflammatory cells and endothelial cells, were used as a positive control. Immunoreactivity to BAF47 was classified into three categories: loss of expression (no staining of tumor nuclei); ±, reduced expression (low-intensity staining of tumor nuclei); +, preserved expression (iso-intensity staining of the nuclei) compared to the positive control. We also performed immunohistochemistry for BAP-1 clone C-4 (mouse monoclonal, dilution 1:50, Santa Cruz Biotechnology, Dallas, USA). Immunohistochemical scoring of BAP-1 expression was performed in a way similar to those published previously [16,17]. BAP-1 staining produced a nuclear signal in all non-neoplastic cells, such as endothelial cells and lymphocytes, and this served as an internal control. BAP-1 loss was identified by a homogenous loss of nuclear staining in tumor cells.

Table 3 Clinicopathologic relationship using Logistic regression univariate analysis

	N	odds ratio	P
Sex			
Male	55	1.000	
Female	9	3.200	.1213
Origin			
Pleura	42	1.000	
Peritoneum	23	3.947	.0339
Age per 1 y/o	74	0.982	.3480
Histologic type			
Deciduoid	9	1.000	
Epithelioid	12	0.045	.0033
Biphasic	36	0.081	.0143
Sarcomatoid	17	0.208	.0734

Table 4 Clinicopathologic relationship using logistic regression multivariate analysis

	N	Odds ratio	P
Origin			
Pleura	42	1.000	
Peritoneum	23	3.257	.1290
Histologic type			
Deciduoid	9	1.000	
Epithelioid	12	0.046	.0170
Biphasic	36	0.106	.0113
Sarcomatoid	17	0.175	.1684

2.3. Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed on formalin-fixed, paraffin-embedded, 4-μm-thick tissue sections. After paraffin sections had been deparaffinized in xylene, dehydrated in ethanol, and air dried, dual-color FISH analysis was performed using a FITC-labeled chromosome 22q centromeric probe and a TexRed–labeled, SMARCB1 dual-color probe (GSP Lab., Inc., Kobe, Japan) together with a SpectrumGreen-labeled chromosome 9 centromeric probe and a Spectrum Orange-labeled, locus-specific CDKN2A (*p16*) probe (Abbott; Abbott Park, IL). Pretreatment steps were performed using a histology FISH accessory kit (Dako Cytomation, Tokyo, Japan) as follows: the section was placed in pretreatment solution (MES; 2-ethanesulphonic acid buffer), incubated at 121°C for 1 minute, and digested with pepsin at 37°C for 5 to 11 minutes. The probes were denatured for 5 minutes at 95°C before hybridization. The slides were then hybridized for 48 hours at 37°C and washed in 2 Å~ SSC/0.3% Tween 20 (Sigma, St Louis, MO) at 78°C for 2 minutes, and finely counterstained with DAPI/antifade (Abbott) [18,21].

2.4. Statistical analysis

Fisher exact test, Logistic regression analysis, the Kaplan–Meier method, and the Wilcoxon test for survival analysis were employed for prognostic factor evaluation (SAS 9.4; SAS Institute, Cary, NC).

3. Results

3.1. SMARCB1/INI1 protein and BAP-1 immunoreactivity

The results of the immunohistochemical analysis are summarized in Table 1. In 17 of the 74 malignant mesotheliomas

(6 cases of the deciduoid type, 5 epithelioid type, 1 biphasic type, and 5 sarcomatoid type), reduced expression of INI1 protein was recognized in all tumor cells compared to the level in positive control samples such as infiltrating lymphocytes and entrapped normal tissue (Fig. 1). Among those 17 cases, 3 cases of the epithelioid type and 2 of the deciduoid type displayed a complete loss of INI1 protein expression. In the biphasic type, both components (epithelioid and sarcomatous type) exhibited reduced expression of INI1. Analysis by histologic type seemed to indicate that reduced expression of INI1 was significantly more frequent in the deciduoid type (6/9: 67%) than in either the epithelioid type (5/36: 14%) or the biphasic type (1/12: 8%) (P = .0033 and P = .0158). However, as the number of cases was small (6 out of 9 cases showing reduced expression of INI1 in the deciduoid type), we can only say that a reduced SMARCB1/INI1 expression *appeared* to be more frequent in the deciduoid type than in either the epithelioid type or the biphasic type.

BAP-1 loss was seen in 6/11 (55%) epithelioid, 6/8 (75%) deciduoid, and 4/6 (67%) biphasic mesothelioma. The relationship between SMARCB1 expression and BAP-1 was analyzed by Fisher exact test. This seemed to indicate a correlation between reduced SMARCB1 expression and loss of BAP-1 expression (P = .0053) (Table 2). However, there were too few cases to warrant further statistical analysis, so no interpretation was attempted regarding correlations within given types of mesothelioma.

3.2. Clinicopathologic analysis

The data obtained were subjected to Logistic regression analysis. A relationship was confirmed between origin (P = .0339) and histologic type (P = .0033 and P = .0143), and the survival period (Table 3). When those factors were entered in to the final models of the multivariate analysis, only histologic type (namely deciduoid type vs epithelioid and biphasic) was found to be a prognostic factor for survival (P = .0170 and P = .0113) (Table 4). According to the Bonferroni test, when there are 4 groups we have to test 6 times, so the standard was below 0.0083 (0.05 divided by 6). There was a statistically significant difference in prognosis between the epithelioid type and sarcomatoid type of malignant mesothelioma (P = .0007, Figs. 2 and 3).

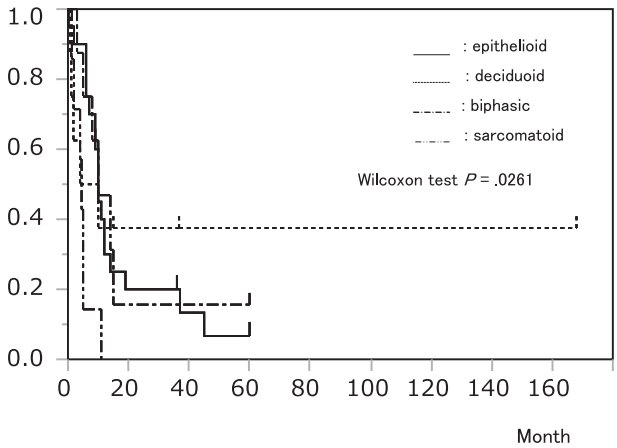

Figure 2 Overall survival of patients with malignant mesothelioma. The prognosis is longer for the deciduoid type than for other histological types.

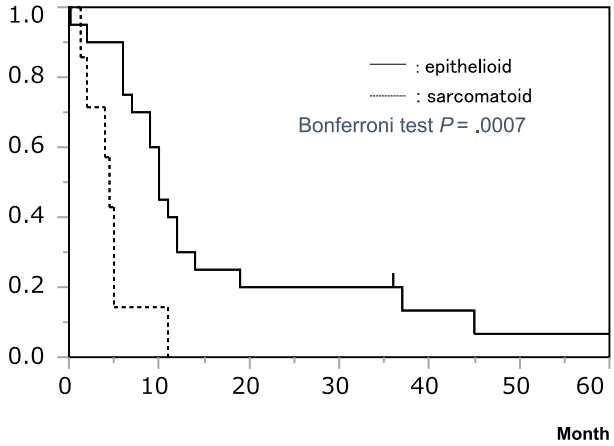

Figure 3 According to the Bonferroni test, the prognosis is longer for epithelioid mesothelioma than for the sarcomatoid type.

3.3. SMARCB1/INI1 and p16 FISH

The mesothelioma cases analyzed here were 8 cases displaying reduced expression of INI1 protein. Only 1 case exhibited homozygous deletion for *INI1* FISH (Fig. 4).

Deletion of p16 was detected by FISH in 0/7 epithelioid, 1/3 deciduoid, and 0/3 biphasic mesotheliomas. No evidence of a correlation between reduced SMARCB1 expression and p16 homozygous deletion could be detected by Fisher exact test (P = .384).

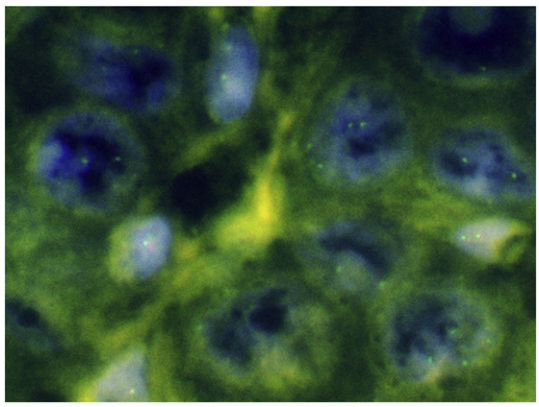

Figure 4 Dual-color FISH analysis was performed using a FITC–labeled chromosome 22q centromeric probe and a TexRed–labeled, SMARCB1 dual-color probe plus a SpectrumGreen-labeled chromosome 9 centromeric probe. Only 1 case showed homozygous deletion for SMARCB1/*INI1* FISH.

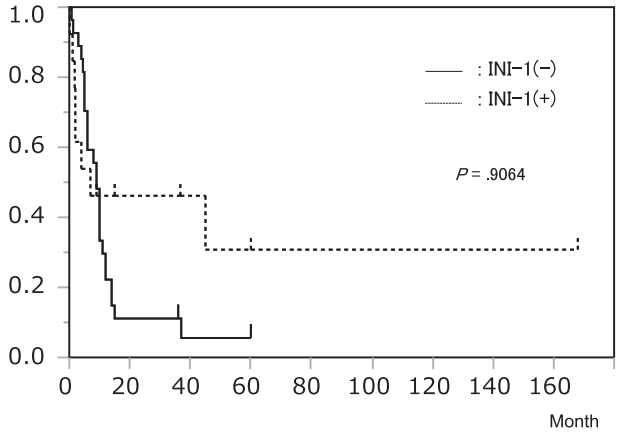

Figure 5 Overall survival of patients in the malignant mesothelioma group with reduced (INI1 ±) or preserved (INI1 +) SMARCB1/INI1 protein expression. There was no statistically significant difference between the two groups (P = .9064).

3.4. Prognosis of malignant mesothelioma according to SMARCB1/INI1 protein expression

Follow-up data were available in 41 of 74 cases (13 reduced INI1 protein expression cases and 28 preserved INI1 protein expression cases). However, there was no statistically significant difference in prognosis between the reduced and preserved cases (P = .9064, Fig. 5).

4. Discussion

Diagnosis of malignant mesothelioma is still challenging (for example, with regard to differential diagnosis of pleural mesothelioma versus lung adenocarcinoma involving the pleura, pleural mesothelioma versus squamous carcinoma of the lung involving the pleura, and pleural mesothelioma versus metastatic renal cell carcinoma), as described in the guidelines for the pathologic diagnosis of malignant mesothelioma [19]. When atypical cells are observed in the pleura or peritoneum, the first step might be to perform immunohistochemistry for BAP-1, and if BAP-1 is not lost to then proceed to p16 FISH [20]. According to Bott et al, there was mutually exclusivity among BAP-1 and CDKN2A losses and mutations, and SMARCB 1 mutation in 53 samples of malignant pleural mesothelioma [21]. Moreover, a case report of SMARCB1-deficient pleural mesothelioma showed neither homozygous deletion of p16 nor BAP-1 protein loss [14]. In the present study, we tried to analyze the relationship between SMARCB1 expression and BAP-1 using Fisher exact test. This seemed to suggest a correlation between reduced SMARCB1 expression and loss of BAP-1 expression (P = .0053) (Table 2). However, because of the small numbers, such a statistical analysis might be misleading as regards correlations within given types of mesothelioma.

In our cases, there was no evidence of a correlation between reduced SMARCB1 expression and p16 homozygous deletion by Fisher exact test (P = .384).

The switch/sucrose non-fermenting (SWI/SNF) complex is a multi-subunit chromatin-remodeling complex consisting of at least 9 proteins with the indication being that several components have tumor-suppressor activity [6,22]. Mammalian cells express the *Drosophila* homeotic gene *brahma* or BRM as well as a closely related protein called Brahma-related gene-1 (BRG1 or SMARCA4). Human BRG1 is approximately 74% identical to human BRM or SMARCA2 [23], 52% identical to *Drosophila* BRM, and 33% identical to yeast SWI2/SNF2 [24]. The mammalian SWI/SNF complexes exist in multiple forms containing 9–12 proteins, and these are referred to as BRM- or BRG1-associated factors or BAFs [25].

Loss of BRG1 (SMARCA4)/BRM has been reported in human lung cancer cell lines and primary lung cancers, and it has also been found that patients with BRG1/BRM-negative carcinomas have a statistically significant decrease in survival compared with patients with BRG1/BRM [26-29]. In terms of histological type, SMARCA4-deficient pulmonary carcinomas are predominantly solid adenocarcinomas and exhibit frankly rhabdoid patterns [30]. Recently, SMARCA4-deficient thoracic sarcomas were also reported to display undifferentiated rhabdoid morphology and to have worse survival than SMARCA4-retained tumors [31,32].

A core subunit of the SWI/SNF complex is SNF5 (also known as INI1 or BAF47 or SMARCB1), which is mutated in children with malignant rhabdoid tumors (MRT) [33]. Loss of INI1/ SMARCB1 was found to be rare (0.46%) in a study of over 3000 colorectal carcinomas, and to be associated with high tumor grade, poor survival, BRAFV600E mutation, and mismatch repair deficiency [34]. Moreover, no evidence of INI1/SMARCB1 mutation was found in a study of 50 human lung cancer cell lines [35].

Deciduoid mesothelioma can be classified into 2 types based on prognosis, according to Ordóñez [4]. In the case of one type, cells exhibited a wide variation in size and shape, frequent loss of cell cohesion, marked nuclear atypia, and high mitotic activity (>5 per 10HPF), whereas in the second type the cells were more cohesive, less pleomorphic, and mitotic activity was low [4]. Ordóñez noted that patient survival was shorter in the first group of cases (mean, 7 months) than in the second group (mean, 23 months). In the present study, 17 of 74 (23%) malignant mesothelioma cases (epithelioid: 24%; biphasic; 8%; sarcomatoid; 29%) exhibited reduced immunohistochemical expression of SMARCB1/INI1 protein. Such a reduced rate of SMARCB1/INI1 expression appeared to be more frequent in the deciduoid type (67%) than in either the epithelioid type or the biphasic type, regardless of the presence or absence of rhabdoid cells, but not significantly different between the deciduoid and sarcomatoid types (P < .1034). However, the present numbers were small (only 6 out of 9 cases displaying reduced expression of INI1 in the deciduoid type), so we can only say that reduced SMARCB1/INI1

expression *tended* to be more frequent in the deciduoid type than in either the epithelioid type or the biphasic type.

Two cases of the deciduoid type with a complete loss of SMARCB1/INI1 protein expression were recognized. However, there was no statistically significant difference in prognosis between malignant mesotheliomas with reduced versus preserved SMARCB1/INI1 protein expression.

As regards SMARCB1/INI1 FISH, only 1 out of 8 cases displayed homozygous deletion. Differences in immunohistochemistry conditions (such as fixation and/or staining procedures) may be factors that caused the observed discrepancy in the frequency of reduced SMARCB1/INI1 expression between 23% of malignant mesotheliomas (the present study) and 0.46% of colorectal carcinomas [34]. Since the above two studies employed the same antibody (BAF47 antibody, clone 25), we can exclude that as a causal factor. We cannot, however, exclude the possibility that the apparent discrepancy reflects a real difference between the two cancer types. It is possible that in deciduoid mesotheliomas with reduced INI1 protein expression, INI1 protein expression is regulated by other post-transcriptional regulatory mechanisms. Indeed, this phenomenon has been seen in other sarcomas such as distal-type epithelioid sarcomas and synovial sarcomas [9,11].

In summary, in this study we are the first to analyze the SMARCB1/INI1 protein expression status in malignant mesothelioma, and we also studied SMARCB1/INI1 FISH. Reduced SMARCB1/INI1 expression appeared to be more frequently in the deciduoid type than in either the epithelioid type or biphasic type. However, larger number of cases will need to be studied to elucidate that point. Only 1 case exhibited homozygous deletion for *INI1* FISH, and there was no statistically significant difference in prognosis between malignant mesotheliomas with reduced versus preserved SMARCB1/INI1 protein expression. The present results do at least suggest that cases displaying reduced SMARCB1/INI1 protein expression should not be excluded from a diagnosis of malignant mesothelioma when performing differential diagnosis. For example, we experienced a case (a young woman with a deciduoid type of mesothelioma in the peritoneum, Fig. 1B) that could have been misdiagnosed as a malignant rhabdoid tumor.

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