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Original contribution

A unique pattern of INI1 immunohistochemistry distinguishes synovial sarcoma from its histologic mimics ☆

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Summary The absence of INI1 (SMARCB1, hSNF5, BAF47) immunohistochemical reactivity is a central feature of malignant rhabdoid tumor, renal medullary carcinoma, and epithelioid sarcoma. We characterized INI1 immunoreactivity in synovial sarcoma (49 cases) in comparison with its closest histologic mimics (68 cases). We observed a unique pattern of decreased INI1 immunoreactivity with a high specificity (100%) and sensitivity (86%) for synovial sarcoma and particular sensitivity for poorly differentiated subtypes of synovial sarcoma (94%; 16/17 cases). Decreased INI1 immunoreactivity was not seen in any of the other lesions we examined, including 14 cases of Ewing sarcoma and 22 cases of malignant peripheral nerve sheath tumor. Furthermore, decreased INI1 immunoreactivity is distinct from the complete absence of INI1 immunoreactivity seen in malignant rhabdoid tumor or other INI1-negative neoplasms. We propose that this distinct INI1 immunohistochemical pattern serves as a useful diagnostic tool to provide preliminary results before molecular test results are available, especially in cases of poorly differentiated synovial sarcoma and in cases where limited material precludes confirmatory molecular studies. Awareness of this unique pattern is critical to avoid misinterpreting decreased INI1 immunoreactivity as a complete absence of INI1 and, consequently, misdiagnosing synovial sarcoma as an INI1-negative neoplasm.

1. Introduction

Synovial sarcoma is histologically classified into biphasic, monophasic fibrous, and poorly differentiated categories [1]. The poorly differentiated category can be further subclassified into epithelioid, small round, or high-grade spindle cell subtypes. These various histologic patterns invoke a wide differential diagnosis that can include small round cell and spindle cell neoplasms [2–4]. Distinguishing poorly differentiated synovial sarcoma from Ewing sarcoma and malignant peripheral nerve sheath tumor (MPNST) can be especially challenging because of overlapping histologic features and immunohistochemical (IHC) reactivity patterns of several markers [4–9]. Few markers can aid in identifying synovial sarcoma (reviewed by Alaggio et al [10]), but definitive diagnosis or exclusion of either synovial sarcoma or Ewing sarcoma often requires specific molecular studies

Abbreviations: IHC, immunohistochemistry; MPNST, malignant peripheral nerve sheath tumor; DSRCT, desmoplastic small round cell tumor; IMT, inflammatory myofibroblastic tumor.

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to detect their characteristic chromosomal translocation or associated fusion transcript. Synovial sarcoma is characterized by a fusion of the *SS18* (*SYT*) gene to an *SSX* family member as the result of a chromosomal translocation, t(X;18) [11–14]. Ewing sarcoma typically contains a chromosomal translocation that results in a fusion of the *EWSR1* gene with an *ETS* family transcription factor [15–17].

The absence of the nuclear tumor suppressor protein INI1 (SMARCB1, hSNF5, BAF47) is a characteristic feature of several neoplasms including malignant rhabdoid tumor, renal medullary carcinoma, and epithelioid sarcoma (reviewed by Hollmann and Hornick [18]). Most of such neoplasms lack INI1 expression due to biallelic deletion or mutation of the *INI1* genomic locus [19–24], resulting in a complete absence of INI1 immunoreactivity. Mosaic biallelic inactivation of *INI1* has also been reported in schwannomas associated with germ-line mutations of INI1 and less frequently in sporadic schwannomas [25,26]. Decreased INI1 immunoreactivity in synovial sarcoma has been identified in a series that examined predominantly monophasic fibrous synovial sarcoma [27]. Given the particular challenge of discriminating poorly differentiated synovial sarcoma from its histologic mimics, we compared the pattern of INI1 immunoreactivity in a series of 49 synovial sarcoma cases enriched in poorly differentiated subtypes (17 cases) with its histologic mimics. We examined Ewing sarcoma, MPNST, and other round or spindle cell lesions, which have not been previously examined, including gastrointestinal stromal tumor (GIST), fibromatosis and inflammatory myofibroblastic tumor (IMT). We show that a unique pattern of diffusely decreased INI1 immunoreactivity in more than 90% of the tumor nuclei is seen in most synovial sarcomas (85.7%), especially poorly differentiated cases (97%). In contrast, all other lesions retain INI1 expression in most of the nuclei (60%-100%). We conclude that decreased INI1 immunoreactivity is a sensitive and specific marker for discriminating synovial sarcoma from other neoplasms, particularly poorly differentiated synovial sarcoma from its closest histologic mimics.

2. Methods

2.1. Case selection

This study was approved by the Office of Human Subject Research of the National Institutes of Health. Cases of synovial sarcoma (49 cases from 40 patients; age range, 9-64 years; average, 32.8 years), Ewing sarcoma (22 cases from 21 patients; age range, 8-34 years; average, 21.0 years), MPNST (14 cases from 13 patients; age range, 10-38 years; average, 24.2 years), IMT (3 cases from 2 patients; age range, 5-21 years; average, 12 years), fibromatosis (4 cases from 4 patients; age range, 15-23 years; average, 18 years), desmoplastic small round cell tumor (DSRCT) (6 cases from 6 patients; age range, 15-30 years; average, 21.8 years), GIST (9 cases from 9 patients; age range, 9-55 years; average, 36.5 years), and leiomyosarcoma (10 cases from 9 patients; age range, 46-69 years; average, 58.3 years) were retrieved from the files of the Department of Pathology of the National Cancer Institute. In addition, 3 cases of malignant rhabdoid tumor and 2 cases of renal medullary carcinoma served as IHC controls. When possible, diagnoses were confirmed by review of available hematoxylin and eosin slides, IHC slides, and available molecular studies. Thirty-two cases of synovial sarcoma (65%) were from 23 patients with confirmatory molecular studies: 8 by *SS18* fluorescence in situ hybridization, 13 by reverse transcriptase polymerase chain reaction (RT-PCR) (8 *SS18-SSX1*, 4 *SS18-SSX2*, and 1 not specified), 1 by conventional cytogenetics, and 1 reportedly confirmed by an unspecified method. Fourteen cases of Ewing sarcoma (64%) were from 14 patients with confirmatory molecular studies: 3 by *EWSR1* fluorescence in situ hybridization and 11 by RT-PCR (8 *EWSR1-FLI1* type 1, 1 *EWSR1-FLI1* type 2, 1 *EWSR1-FLI1* variant, and 1 with no type specified). Four cases of DSRCT (67%) were from 4 patients with confirmatory molecular studies: 3 by *EWSR1-WT1* RT-PCR and 1 by conventional cytogenetics. Nine of the 14 MPNST cases originated from patients with neurofibromatosis type 1. Available clinicopathologic data were tabulated.

2.2. INI1 Immunohistochemistry

IHC staining was performed on paraffin-embedded tissues using the EnVision +DAB system (Dako, Carpinteria, CA) according to manufacturer's instructions. Sections underwent microwave pressure cooker antigen retrieval in Target Retrieval Solution, Citrate pH 6 (Dako, Carpinteria, CA) for 10 minutes. Purified mouse anti-BAF47 (INI1), clone 25/BAF47 (BD Biosciences, San Jose, CA), was applied for 1 hour at room temperature at 1:100 concentration. In all cases, INI1 immunoreactivity of neoplastic nuclei was compared with that of intervening stromal and endothelial cell nuclei within the same microscopic field at 10× or greater objective magnification. If strong immunoreactivity of stromal or endothelial nuclei was not present, the specimen was considered technically inadequate and not scored. Tumor cell nuclei evaluated as having preserved INI1 immunoreactivity showed INI1 immunoreactivity at least as intense as the adjacent stromal and endothelial cell nuclei. Decreased INI1 immunoreactivity was characterized by tumor nuclei with less intense INI1 immunoreactivity than the adjacent stromal and endothelial cell nuclei. The percentage of tumor cells with decreased INI1 immunoreactivity was evaluated and recorded by 2 pathologists in all tumors in the study.

2.3. Statistical methods

All P values for comparison of immunoreactivity results were calculated using the χ^2 test. Specificity represents the percentage of cases with decreased INI1 immunoreactivity

that are synovial sarcoma. Sensitivity represents the percentage of synovial sarcoma cases that showed decreased INI1 immunoreactivity.

3. Results

3.1. Decreased INI1 immunoreactivity is unique to synovial sarcoma

Forty-two (85.7%) of 49 cases of synovial sarcoma showed decreased INI1 immunoreactivity in at least 90% of the neoplastic nuclei relative to the intervening internal control stromal and endothelial nuclei (Fig. A and B). This decrease tended to be uniform within each case and was typically a qualitatively marked decrease in INI1 immunoreactivity (Fig. A) in all but 4 cases, which showed a mild decrease (Fig. B). In contrast, all 22 Ewing sarcoma and all 14 MPNST cases showed preserved INI1 immunoreactivity in most neoplastic nuclei, with less than 10% of the neoplastic nuclei showing decreased or absent INI1 immunoreactivity (Fig. C and D). Similarly, all other tumor types examined showed preserved expression, with low percentages of tumor nuclei showing decreased INI1 immunoreactivity, varying from less than 10% in all 6 DSRCT cases, to less than 20% in all 4 fibromatosis cases, to less than 30% in all 3 myofibroblastic tumor and all 9 GIST cases and less than 40% in all 10 leiomyosarcoma cases (Fig. E). Importantly, INI1 immunoreactivity in synovial sarcoma was never uniformly and completely absent, unlike the complete absence of INI1 immunoreactivity seen in malignant rhabdoid tumor (Fig. F). Decreased INI1 immunoreactivity was 100% specific and 85.7% sensitive for synovial sarcoma, and differences among the examined neoplasm types were statistically significant (Table 1). Seven synovial sarcoma cases (14.3%) showed preserved INI1 immunoreactivity in more than 80% of the tumor nuclei. Three of these cases were from 3 different patients with confirmatory molecular studies. Of note, INI1 immunoreactivity typically showed some heterogeneous intensity in normal tissues (open arrows in Fig.).

3.2. Decreased INI1 immunoreactivity is characteristic of all histologic categories of synovial sarcoma

All 3 histologic categories of synovial sarcoma [1,28] showed decreased INI1 immunoreactivity: biphasic (5/5 cases), monophasic fibrous (21/27 cases), and poorly differentiated (16/17 cases). Differences in the frequency of the decreased INI1 immunoreactivity pattern did not reach statistical significance among these categories. Importantly, nearly all cases of poorly differentiated synovial sarcoma showed decreased INI1 immunoreactivity: 12 of 13 poorly differentiated spindle cell cases and 4 of 4 poorly differentiated round cell cases. The frequency of decreased INI1 immunoreactivity in poorly differentiated subtypes of synovial sarcoma was significantly different from each of its corresponding histologic mimics (Table 2). All 4 synovial sarcoma cases with a mild decrease in INI1 immunoreactivity and 6 of the 7 cases with preserved INI1 immunoreactivity were of the monophasic fibrous category. One case with preserved INI1 immunoreactivity was a poorly differentiated spindle cell subtype. Confirmatory molecular studies were available in all 4 cases with mildly decreased and in 3 of the 7 cases with preserved INI1 immunoreactivity: 2 of the monophasic fibrous cases and the poorly differentiated spindle cell case.

3.3. Serial biopsies of synovial sarcoma may show different INI1 immunoreactivity

Six patients were represented by multiple biopsies, contributing 15 total cases. Thirteen (86.7%) of these 15 cases showed decreased INI1 immunoreactivity (1 mild decrease, 12 marked decrease). The 2 cases with preserved INI1 immunoreactivity originated from 2 different patients. Interestingly, other specimens from these 2 patients showed decreased INI1 immunoreactivity. One of these patients had an initial biopsy showing monophasic fibrous synovial sarcoma with decreased INI1 immunoreactivity. One month later, a follow-up biopsy at the same anatomical site showed similar histology and preserved INI1 immunoreactivity. The second patient had an initial biopsy showing poorly differentiated spindle cell synovial sarcoma with preserved INI1 immunoreactivity. Two and 3 years later, respectively, follow-up biopsies of 2 metastatic sites showed monophasic fibrous histology and decreased INI1 immunoreactivity. In at least 1 site from each of these patients, the diagnosis of synovial sarcoma was confirmed by RT-PCR. Of note, the frequency of decreased INI1 immunoreactivity in patients with multiple cases (13/15 cases; 86.7%) is similar to patients represented by a single case (29/34 cases; 85.3%).

4. Discussion

The diverse histologic appearances of synovial sarcoma, combined with the possibility of rhabdoid features [27], can mimic many neoplasms. Distinguishing synovial sarcoma from Ewing sarcoma and MPNST is further complicated by the significantly overlapping IHC features of these lesions [4–9]. In this series, we studied INI1 immunoreactivity in 49 cases of synovial sarcoma, including 17 poorly differentiated cases, in comparison with selected histologic mimics: Ewing sarcoma (22 cases), MPNST (14 cases), IMT (3 cases), fibromatosis (4 cases), DSRCT (6 cases), GIST (9 cases), leiomyosarcoma (10 cases), and control cases of malignant rhabdoid tumor. We report decreased INI1 immunoreactivity in synovial sarcoma (42/49 cases), which was not seen in any

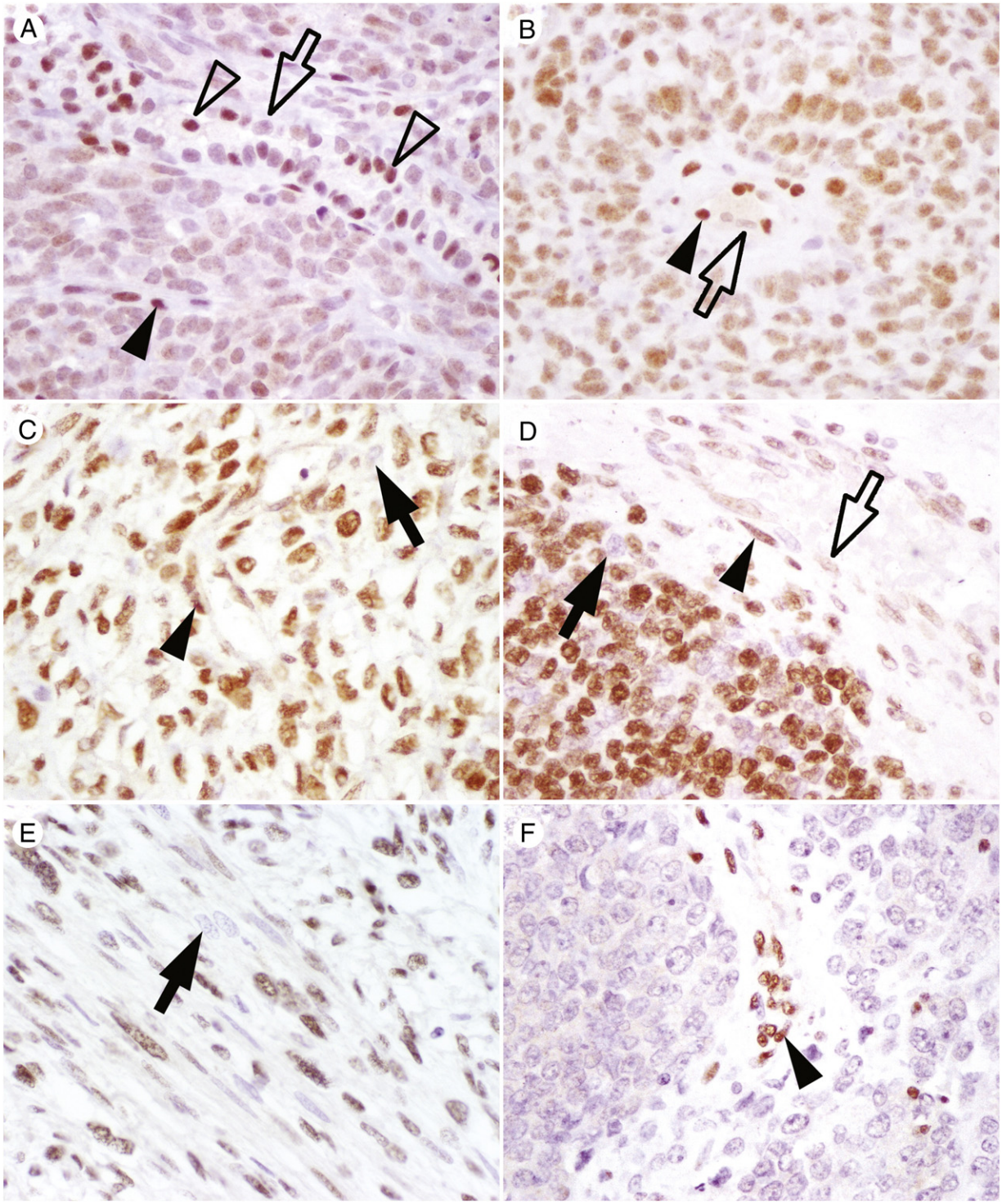

Fig. INI1 Immunohistochemistry. Synovial sarcoma most often showed uniformly decreased INI1 immunoreactivity compared with the intervening stromal and endothelial nuclei. The degree of the reduction varied from markedly decreased (A) to mildly decreased (B). All cases of MPNST (C), Ewing sarcoma (D), and leiomyosarcoma (E) showed strong INI1 immunoreactivity, with occasional less intensely stained nuclei (filled arrows). The pattern of decreased INI1 immunoreactivity is distinct from the complete absence of nuclear immunoreactivity seen in malignant rhabdoid tumor (F). Note that the strong INI1 immunoreactivity in entrapped alveolar epithelium (open arrowheads) and endothelial nuclei (filled arrowheads) stands out from the INI1 immunoreactivity of neoplastic nuclei, and some variation in immunoreactivity of these normal cell types is also seen (open arrows). (A-F, magnification ×400.)

Table 1 Immunoreactivity of synovial sarcoma and its closest histologic mimics

	INI1 expression		% Decreased
	Preserved	Decreased	
Synovial sarcoma	7	42	85.7
Ewing Sarcoma	22	0	0 [a]
DSRCT	6	0	0 [b]
MPNST	14	0	0 [c]
GIST	9	0	0 [d]
IMT	3	0	0 [e]
Fibromatosis	4	0	0 [f]
Leiomyosarcoma	10	0	0 [g]

NOTE. Decreased INI1 immunoreactivity is seen in synovial sarcoma and not in the other neoplasms examined. The differences between synovial sarcoma and its potential mimics are statistically significant:

[a] $P < 10^{-10}$.
[b] $P < 10^{-5}$.
[c] $P < 10^{-8}$.
[d] $P < 10^{-6}$.
[e] $P < .002$.
[f] $P < 10^{-4}$.
[g] $P < 10^{-7}$.

Table 2 Decreased immunoreactivity of INI1 IHC distinguishes Ewing sarcoma and MPNST from synovial sarcoma with similar histologic features

	INI1 expression		% Decreased
	Preserved	Decreased	
Poorly differentiated round cell synovial sarcoma	0	4	100.0
Ewing sarcoma	22	0	0 [a]
DSRCT	6	0	0 [b]
Poorly differentiated spindle cell synovial sarcoma	1	12	91.6
MPNST	14	0	0 [c]
GIST	9	0	0 [d]
IMT	3	0	0 [e]
Fibromatosis	4	0	0 [e]
Leiomyosarcoma	10	0	0 [d]

NOTE. Immunoreactivity of poorly differentiated synovial sarcomas and their closest histologic mimics. The differences between synovial sarcoma and its potential mimics are statistically significant:

[a] $P < 10^{-6}$.
[b] $P < .002$.
[c] $P < 10^{-5}$.
[d] $P < 10^{-4}$.
[e] $P < 10^{-3}$.

of the 68 cases of other histologically similar neoplasms we examined. The pattern of decreased INI1 immunoreactivity was distinct from the complete absence seen in the nuclei of malignant rhabdoid tumor and from the mosaic absence of INI1 reported in schwannomas [25,26]. The distinction between synovial sarcoma and neoplasms with preserved INI1 immunoreactivity can be made based on the dramatic differences in the percentage of neoplastic nuclei with decreased INI1 immunoreactivity; 90% to 100% in synovial sarcoma compared with 0 to 10% in the closest histologic mimics (Ewing sarcoma, MPNST, and DSRCT), or compared with 20% to occasionally 40% in other spindle cell lesions. The decreased INI1 immunoreactivity characteristic of synovial sarcoma tended to show a uniformly decreased intensity, allowing the strong staining of normal stromal and vascular cells to stand out from the neoplastic cells, and was seen in all histologic subtypes of synovial sarcoma. Importantly, decreased INI1 immunoreactivity was seen in nearly all cases of poorly differentiated synovial sarcoma (16/17 cases), which can present the greatest challenge to discriminate from other neoplasms. This resulted in significant differences when comparing the poorly differentiated round cell subtype of synovial sarcoma with Ewing sarcoma or DSRCT, and when comparing the poorly differentiated spindle cell subtype of synovial sarcoma with spindle cell lesions such as MPNST, GIST, leiomyosarcoma, and fibromatosis. Similarly, spindle epithelial tumor with thymus-like differentiation, a rare tumor of the thyroid that can mimic synovial sarcoma, can be distinguished from synovial sarcoma by preserved INI1 immunoreactivity in most cases of spindle epithelial tumor with thymus-like differentiation [29].

In our series, decreased INI1 immunoreactivity demonstrated high specificity (100%) and sensitivity (85.7%) for synovial sarcoma. We confirmed the unique pattern of reduced INI1 reactivity in synovial sarcoma that was previously reported by Kohashi et al [27] and expanded the list of studied lesions to include GIST, IMT, and fibromatosis. We observed a significantly higher overall frequency of decreased INI1 immunoreactivity in synovial sarcoma than did Kohashi et al (85.7% versus 69.7%, $P = .0046$), yet comparison of the smaller numbers of cases in each histologic group between these series did not reach statistical significance (monophasic fibrous $P = .16$, biphasic $P = .59$, and poorly differentiated $P = .24$). Although the difference in our overall results may be influenced by the increased frequency of confirmatory molecular testing in our series (65% compared with 42%), it is most likely related to the differences in the proportion of poorly differentiated synovial sarcoma cases. We examined a higher proportion of poorly differentiated cases of synovial sarcoma (17/49 compared with 4/95 by Kohashi et al), a group with the highest frequency of decreased INI1 immunoreactivity (16/17 in our series compared with 3/4 in that of Kohashi et al). Our series greatly adds to our understanding of the utility of INI1 IHC in synovial sarcoma, especially in distinguishing poorly differentiated synovial sarcoma from its closest histologic mimics.

Unexpectedly, we found that serial biopsies of synovial sarcoma resulted in different INI1 immunoreactivity. A similar phenomenon was previously reported in 1 patient [30]. In our series, 2 of the 7 synovial sarcoma cases with

preserved INI1 immunoreactivity originated from 2 patients with additional cases that showed decreased INI1 immunoreactivity. In our data, decreased INI1 immunoreactivity is seen as often in patients represented by only a single case (85.3%) as in cases from patients with multiple specimens (86.7%). From our limited available clinical data, we cannot identify a clear pattern that suggests an explanation for the variations in INI1 immunoreactivity seen in biopsies from the same patient. These variations are unlikely related to case fixation and processing because stromal and endothelial nuclei within each tissue served as internal controls. It remains possible that these differences represent clonal variations in these neoplasms or are related to therapeutic interventions. Despite our incomplete understanding of this phenomenon, awareness of this variation is key to avoid incorrectly excluding the diagnosis of synovial sarcoma based on a preserved INI1 immunoreactivity. Further studies of serial biopsies are needed to clarify the frequency and significance of these observations.

Although the mechanism that governs the decreased INI1 immunoreactivity seen in synovial sarcoma remains unclear, available evidence points to posttranscriptional control of *INI1* in synovial sarcoma. Because INI1 reactivity in synovial sarcoma is not absent in a subset of neoplastic cells but, instead, is uniformly decreased, biallelic inactivation of the *INI1* locus seen in other neoplasms cannot explain this phenomenon. Given the specificity of decreased INI1 immunoreactivity for synovial sarcoma, the mechanism that controls this IHC phenotype may be related to globally altered gene regulation caused by the SS18-SSX fusion protein [31], which is pathognomonic of synovial sarcoma. Evaluations of *INI1* messenger RNA levels in synovial sarcoma have shown that the expression of *INI1* messenger RNA is increased, demonstrating that a posttranscriptional mechanism is responsible for the observed reduction of INI1 protein [27]. This mechanism could involve either regulation of translation, possibly by a microRNA, or regulation of INI1 protein degradation. Both mechanisms are conceivable because the SS18-SSX fusion protein is known to regulate other genes by either modulating microRNA expression [32,33] or protein ubiquitination and degradation [34]. Understanding *INI1* regulation may shed light on gene regulation by the SS18-SSX fusion protein in synovial sarcoma.

In summary, we report that uniformly decreased INI1 immunoreactivity is highly sensitive and specific for synovial sarcoma. To our knowledge, this pattern has not been reported in any other neoplasm. We demonstrate that this pattern is distinct from the patterns of INI1 expression in common histologic mimics of synovial sarcoma. Therefore, we propose that INI1 IHC can be a useful diagnostic tool for detecting synovial sarcoma. Although INI1 IHC cannot replace molecular testing, recognition of decreased INI1 immunoreactivity as a specific pattern in synovial sarcoma can guide selection of subsequent molecular tests and can help reach a diagnosis in cases with limited biopsy material not amenable to molecular studies, particularly in poorly differentiated synovial sarcoma. Awareness of this unique IHC pattern is critical to avoid the diagnostic pitfall of misinterpreting a marked reduction of INI1 immunoreactivity in synovial sarcoma as negative, leading to an incorrect differential diagnosis. Lastly, studying the regulation of INI1 in synovial sarcoma may provide biologic insights into synovial sarcoma, with potential impacts on treatment, management, and prognosis.

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