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INI1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas

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Rhabdoid cells are encountered in specific entities, such as malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor, as well as in composite rhabdoid tumors derived secondarily from other tumor types. Although rhabdoid tumors are uniformly aggressive, distinction of the entity from the phenotype remains important for its therapeutic implications. The majority of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors affect infants and young children, harbor chromosome 22q deletions, and inactivate the *INI1/hSNF5/BAF47* tumor suppressor gene on 22q11.2. In contrast, most composite rhabdoid tumors are diagnosed in adults, with FISH detectable 22q losses the exception rather than the rule. However, this assay remains limited since 22q dosages are maintained in 20–30% of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors. Furthermore, chromosome 22 losses are common in some parent tumor types, particularly meningiomas. The recently developed INI1 antibody shows loss of nuclear expression in malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors, though its status in composite rhabdoid tumors is largely unknown. Therefore, we utilized immunohistochemistry and FISH to study INI1 expression and 22q dosages, respectively, in 40 composite rhabdoid tumors, including 16 meningiomas, 15 carcinomas, three melanomas, two sarcomas, two glioblastomas, and 1 neuroblastoma. Approximately 70% of rhabdoid meningiomas had a 22q deletion, but this was rare in other tumor types. Except for one retroperitoneal leiomyosarcoma, nuclear INI1 expression was retained in all composite rhabdoid tumors, including meningiomas with 22q deletion. Therefore, we conclude that INI1 immunohistochemistry is a relatively simple, sensitive, and specific technique for distinguishing malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor from composite rhabdoid tumor.
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The designation of a neoplasm as 'rhabdoid' in type relies on the presence of large epithelioid cells with eccentric eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and globular/fibrillar paranuclear inclusions corresponding ultrastructurally to whorled bundles of intermediate filaments. Even in the absence of the paranuclear inclusion though, the cytologic features are sufficiently characteristic to raise the possibility of a rhabdoid neoplasm. These cellular findings were initially described in malignant rhabdoid tumor of the kidney[1,2] and were designated 'rhabdoid' based on their resemblance to rhabdomyoblasts, but lack of ultrastructural evidence for skeletal muscle differentiation. This cell type was subsequently identified in many extrarenal sites and tumor types, leading to considerable debate regarding issues of nomenclature and histogenesis.[3–7] However, accumulating data suggest that rhabdoid tumors exist as both a specific entity and a secondary morphologic phenotype encountered within a wide array of tumor types, typically signifying the emergence of cytologic anaplasia, high-grade features, and aggressive biology. The two generally accepted diagnostic entities are malignant rhabdoid tumor (renal and extrarenal

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forms) and atypical teratoid/rhabdoid tumor of the central nervous system.[2,8–14] Both malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor have a distinct predilection for infants and young children (including congenital and disseminated presentations), a highly aggressive biology with short survival times, a polyphenotypic immunoprofile, and characteristic deletions and mutations (somatic or germline) involving the *INI1/hSNF5* tumor suppressor gene on chromosome 22q11.2.[11,15–24] Although the histogenesis is unknown, it is likely that the malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor represent the same basic neoplasm, differing only in the appellation assigned for different sites of origin. The secondary rhabdoid phenotype is most often found in neoplasms of adults and has been encountered in a variety of parent neoplasms, including carcinomas, melanomas, sarcomas, desmoplastic small round cell tumors, neuroblastomas, meningiomas, and gliomas.[7,25–34] Occasionally, the parent tumor is not immediately recognizable so that a specific diagnosis is not attainable, beyond that of a high-grade malignant neoplasm. Previously referred to as composite extrarenal rhabdoid tumors, the 'extrarenal' portion is no longer appropriate, given the recent recognition of a rhabdoid variant of renal cell carcinoma.[27,33] Therefore, we currently refer to them simply as composite rhabdoid tumors.

For reasons that are poorly understood, rhabdoid cytology is nearly universally associated with aggressive behavior. A recent study suggested that loss of INI1/hSNF5 function affects the actin cytoskeleton, providing a potential explanation for the rhabdoid morphology itself.[35] Another study suggests that cytokeratin 8 gene (*KRT 8*) mutations result in the formation of intracytoplasmic intermediate filament inclusions.[36] Therefore, it is possible that the rhabdoid morphology may arise through similar molecular mechanisms regardless of the histogenesis. Nevertheless, distinguishing composite rhabdoid tumors from malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors remains important given differences in therapeutic approach. For the former, patient management typically follows the guidelines of the parent neoplasm, whereas for the latter, an extremely aggressive protocol with high-dose chemotherapy and stem cell rescue has been advocated.[14] In most examples, the clinicopathologic features are sufficiently specific to clearly distinguish one from the other (Table 1). Using immunohistochemistry, the majority of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors have a polyphenotypic immunoprofile that includes epithelial membrane antigen (EMA), vimentin, smooth muscle actin, and CD99 positivity, as well as variable immunoreactivities for cytokeratins, glial fibrillary acidic protein (GFAP), synaptophysin, neurofilament, S-100 protein, and desmin. In contrast, most composite rhabdoid tumors retain the same or a slightly altered immunoprofile of the parent neoplasm. However, there remains sufficient clinical, morphologic, and immunohistochemical overlap such that a subset of cases are problematic. This is further complicated by the fact that PNET-like, carcinoma-like, and sarcoma-like foci are all common in malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors, occasionally predominating over the rhabdoid cells. We have previously shown that FISH analysis for the detection of 22q deletions is a useful technique in this differential diagnosis and is applicable to formalin-fixed paraffin-embedded tissue.[7,9,20] Nevertheless, this assay is limited by the fact that it is not yet widely available, 20–30% of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors have no detectable deletions, and occasional composite rhabdoid tumors harbor deletions.[7] The latter is particularly relevant for parent tumors that normally have a high frequency of 22q deletions, such as meningioma.

Recently, a commercial antibody for the INI1/BAF47 protein has become available and shows widespread nuclear positivity in normal cells, including endothelial cells and lymphocytes. The latter thus provide a useful internal control. Loss of nuclear expression has been universally encountered in malignant rhabdoid tumor and atypical

Table 1 Features favoring malignant rhabdoid tumor or atypical teratoid/rhabdoid tumor *vs* composite rhabdoid tumor

Parameter	*Malignant rhabdoid tumor or atypical teratoid/rhabdoid tumor*	*Composite rhabdoid tumor*
Patient age	Child (<3 years)	Adult
Location of tumor	Kidney, brain, soft tissue	Extrarenal visceral organs, dura, skin
Histology	Mixed carcinoma, PNET, and/or sarcoma-like foci	Recognizable parent neoplasm
Immunohistochemistry	Polyphenotypic profile, loss of INI1 expression	Single lineage profile, retained INI1[a]
Ultrastructure	Lack of differentiation	Differentiation consistent with parent neoplasm
Genetics	22q deletions common, *INI1* mutations, homozygous deletions	22q deletions uncommon, genetic features of parent neoplasm

[a]Based on data from current study.

teratoid/rhabdoid tumor, but not in the majority of other pediatric central nervous system (CNS) and soft tissue tumors.[23,24] However, this marker has not yet been applied to composite rhabdoid tumors, where it may be particularly useful as an ancillary diagnostic aid. It would also potentially serve a second role in clarifying a basic biologic question for rhabdoid neoplasms. One of the hypotheses states that rhabdoid cytology represents a common end-stage pattern in a histogenetically diverse group of tumors. If that is true, then loss of INI1 expression could conceivably represent the common substrate. Therefore, in the current study, we performed INI1 immunohistochemistry on 40 archival, paraffin-embedded composite rhabdoid tumors derived from 16 meningiomas, 15 carcinomas, three melanomas, two sarcomas, two glioblastomas, and one neuroblastoma. Our data suggest that composite rhabdoid tumors are genetically distinct from malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor and retain INI1 expression in the majority of cases, including meningiomas and other tumors with chromosome 22q deletions.

Materials and methods

The surgical files of the Lauren V Ackerman Laboratory of Surgical Pathology and consultation files of two of the authors (AP, LPD) were searched for the term 'rhabdoid' within the diagnostic line of cases signed out between 1994 and 2004. Those cases arising within a recognizable parent neoplasm (ie composite rhabdoid tumors) were retrieved for further study. A representative paraffin block was cut at 5 μm onto positively charged glass slides for immunohistochemistry and FISH analysis. In consult cases lacking an available paraffin block, archived unstained sections were utilized if available.

Immunohistochemistry was performed as previously published,[23,24] utilizing the BAF47/SNF5 mouse monoclonal antibody (BD Transduction Labs, San Diego, CA, USA) and DAKO autostainer® (Carpinteria, CA, USA). Slides were subjected to heat-induced epitope retrieval pretreatment in citrate buffer (pH 6.0) for 3 min, followed by cooling to room temperature. Sections were incubated with primary antibody at a 1:40 dilution for 30 min at room temperature. Detection was performed utilizing the DAKO Envision Plus HRP secondary anti-mouse antibody, 3,3-diaminobenzidine (DAB), and counterstaining with hematoxylin.

FISH analysis was performed as previously published[7] using DNA probes for BCR on 22q11.2 (SpectrumGreen-labeled; Vysis, Inc., Downers Grove, IL, USA) and NF2 on 22q12 (rhodamine-labeled; paired cosmid probes n3022 and n24f20, UK HGMP Resource Centre, http://www.hgmp.mrc.ac.uk; gift from Dr Mia MacCollin, Massachusetts General Hospital, Boston, MA, USA). The BCR probe is located within 0.5 Mb of the *INI1* gene and is known to be codeleted in the majority of cases of malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor. Sections were deparaffinized, steamed in 10 mM citrate buffer, pH 6.0, and pepsin digested. Paired probes were codiluted to concentrations of 1:25 in DenHyb buffer (Insitus Laboratories, Albuquerque, NM, USA) and 10 μl was applied to each slide. Target and probe DNA were codenatured at 90°C for 13 min. Hybridization was carried out via overnight incubation at 37°C in a humidified oven and the following day, the slides were washed with 50% formamide/1 × SSC, followed by two washes in 2 × SSC for 5 min each. Nuclei were counterstained with DAPI and fluorescent signals were enumerated under an Olympus BX60 fluorescent microscope with appropriate filters (Olympus; Melville, NY, USA). For each hybridization, 100 nonoverlapping nuclei were assessed for numbers of green and red signals. Cutoffs for BCR and NF2 deletions were each set at 50% nuclei with one signal (mean plus 3 s.d. for non-neoplastic control nuclei with one signal). Hybridizations were considered noninformative if the FISH signals were either lacking or too weak to interpret.

Results

Clinicopathologic, immunohistochemical, and available genetic data on the 40 cases of composite rhabdoid tumor are summarized in Table 2. A total of 12 cases were published in a prior study.[7] The parent neoplasms included 16 meningiomas, 15 carcinomas, three melanomas, two sarcomas, two glioblastomas, and one neuroblastoma. The 23 female and 17 male patients ranged in age from 3 months to 80 years (median 60 years) and included 4 children (<18 years of age).

By immunohistochemistry, 38 of 39 (97%) informative cases showed retention of nuclear INI1 expression (Table 2; Figure 1a–f). Although there was regional variability in staining intensities, foci of strong tumoral and/or nontumoral nuclear staining were seen in nearly all tested cases. The three cases considered noninformative had lack of staining within endothelial cells or lymphocytes, or variable expressivity. One retroperitoneal leiomyosarcoma showed loss of INI1 expression in tumor nuclei, with appropriate staining of intratumoral endothelial cells serving as the internal control (Table 2; Figure 1g,h).

Deletions of 22q were identified in 11 of 34 (32%) cases assessed by FISH (Table 2, Figure 2). All but one of the cases with 22q deletions were meningiomas, with rhabdoid meningiomas showing 22q deletion in 10 of 14 (71%) cases overall. The 23 nondeleted cases of composite rhabdoid tumor harbored either normal 22q dosages or gains in copy numbers (polysomy) (Table 2, Figure 2). None

Table 2 Summary of clinicopathologic, immunohistochemical and FISH data

Case	*Age/sex*	*Parent tumor*	*Organ*	*22q FISH*	*INI1*
1	3 mo/M	Angiosarcoma	Soft tissue	Normal	Retained
2[a]	64/M	Carcinoma	Lung	Polysomy	Retained
3[a]	54/M	Carcinoma	Small bowel	*Deleted*	Retained
4[a]	42/M	Carcinoma	Kidney	Polysomy	NI
5[a]	72/F	Carcinoma	Uterus	Polysomy	Retained
6[a]	68/F	Carcinoma	Kidney	Normal	Retained
7[a]	66/F	Carcinoma (lung)	Femoral metastasis	Normal	Retained
8	41/F	Carcinoma	Liver	ND	Retained
9	52/F	Carcinoma	Uterus	Normal	Retained
10	79/F	Carcinoma	Kidney	Normal	Retained
11	66/M	Carcinoma	Kidney	Normal	Retained
12	68/F	Carcinoma	Kidney	Normal	Retained
13	68/F	Carcinoma	Kidney	Polysomy	Retained
14	53/F	Carcinoma	Lung	Polysomy	Retained
15	57/M	Carcinoma	Kidney	Polysomy	Retained
16	60/M	Carcinoma	Kidney	NI	Retained
17	36/M	Glioblastoma	Brain	ND	NI
18	20/F	Glioblastoma	Brain	ND	NI
19	29/M	Leiomyosarcoma	Soft tissue	Normal	*Lost*
20	80/M	Melanoma (skin)	Lung metastasis	Normal	Retained
21[a]	46/F	Melanoma	Skin	Polysomy	Retained
22[a]	21/M	Melanoma	Skin	Polysomy	Retained
23[a]	60/F	Melanoma (skin)	Bone metastasis	Polysomy	Retained
24	78/M	Meningioma	Brain	ND	Retained
25[a]	65/M	Meningioma	Brain	*Deleted*	Retained
26	61/F	Meningioma	Brain	*Deleted*	Retained
27[a]	65/F	Meningioma	Brain	Normal	Retained
28	36/M	Meningioma	Brain	*Deleted*	Retained
29	68/F	Meningioma	Brain	*Deleted*	Retained
30	42/F	Meningioma	Brain	*Deleted*	Retained
31	37/F	Meningioma	Brain	Normal	Retained
32	79/F	Meningioma	Brain	*Deleted*	Retained
33	52/F	Meningioma	Brain	*Deleted*	Retained
34	23/M	Meningioma	Brain	Normal	Retained
35	8/M	Meningioma	Brain	Normal	Retained
36	59/F	Meningioma	Brain	*Deleted*	Retained
37	60/F	Meningioma	Brain	ND	Retained
38	15/F	Meningioma	Brain	*Deleted*	Retained
39	31/F	Meningioma	Brain	*Deleted*	Retained
40[a]	7 mo/M	Neuroblastoma	Adrenal	Normal	Retained

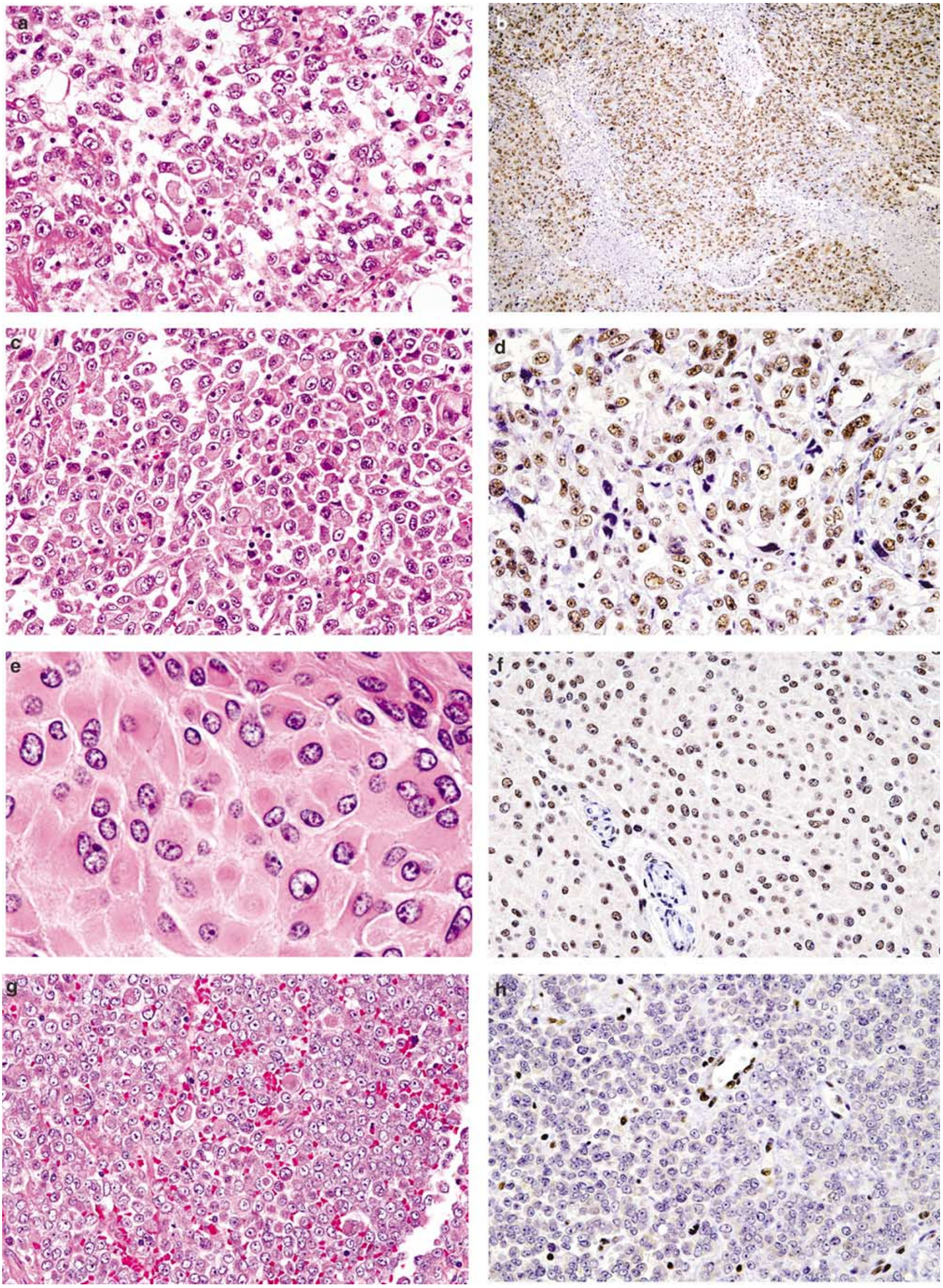
[a]Cases previously published in Fuller *et al*.[7]
NI = noninformative; ND = not done. Age is expressed in years except in two instances mentioned with mo. mo = months.

of the 11 cases with 22q deletion had a concomitant loss of INI1 expression. Similarly, the single case of leiomyosarcoma with loss of protein expression showed no associated 22q deletion by FISH. Mutation screening of paraffin-embedded tissue from this case was attempted, but was unsuccessful.

Discussion

Despite the rarity of malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor, these aggressive tumors of infants and young children have engendered considerable interest with much progress made over the last 5–10 years in elucidating the biology and genetics.[4–36] Although the histogenesis remains uncertain, these tumors are generally considered to be a form of primitive or embryonal neoplasm with a distinctive polyphenotypic immunoprofile, usually including combinations of EMA, vimentin, smooth muscle actin, and CD99 expression. Nevertheless, given their remarkably wide morphologic and immunohistochemical spectrum with varying numbers of rhabdoid cells in any one tumor, they can be diagnostically challenging. Composite rhabdoid tumors are similarly challenging, since

Figure 1 Examples of H&E (**a**, **c**, **e**, **g**) and INI1 (**b**, **d**, **f**, **h**)-stained sections from composite rhabdoid tumors derived from a lung carcinoma (**a**, **b**), a renal cell carcinoma (**c**, **d**), a meningioma (**e**, **f**) and a leiomyosarcoma (**g**, **h**). Nuclear INI1 expression was retained in the first three of these (**b**, **d**, **f**). In contrast, there was loss of expression in the leiomyosarcoma, with appropriate staining of intratumoral endothelial cell nuclei (**h**).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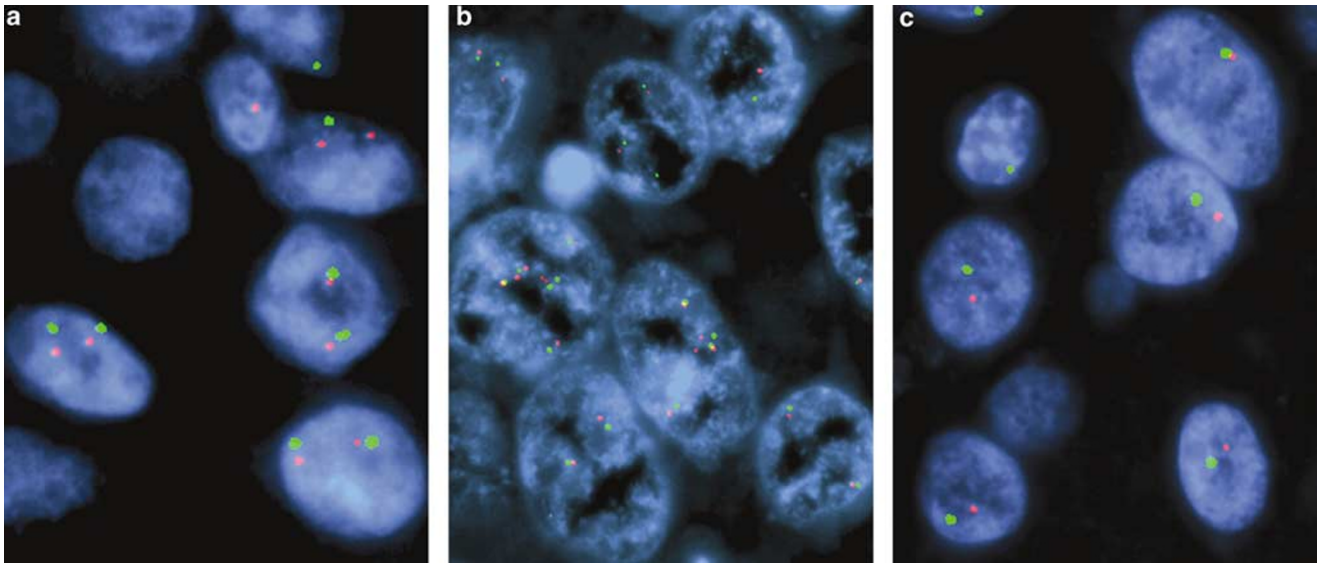

Figure 2 Representative FISH images from three cases of composite rhabdoid tumor showing normal 22q dosages with two green BCR and two red NF2 signals (**a**), polysomy 22q with >2 green and >2 red signals (**b**), and 22q deletion with one green and one red signal in most nuclei (**c**).

they are typically highly anaplastic tumors and the parent neoplasm is not always readily appreciable. Given the nearly uniformly poor prognosis, some have speculated that rhabdoid cells merely represent an end-stage phenotype, rather than a specific entity. However, recent data have shown that malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor, in particular, share a characteristic genetic background with biallelic inactivation of the *INI1/hSNF5* tumor suppressor gene on chromosome 22q11.2 in most cases.[15–24] A congenital disseminated form has also been recognized and is often associated with mutations of the same gene.

Although its function remains to be fully elucidated, the INI1 protein product has been identified as a member of the SWI/SNF multiprotein complex involved in chromatin remodeling.[22] It is ubiquitously expressed in non-neoplastic nuclei and therefore, intratumoral endothelial cells and lymphocytes provide a useful internal control for immunohistochemical studies. An antibody applicable to routinely processed paraffin-embedded tissue has recently been developed and studies have shown uniform INI1 loss in malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor.[23,24] In the current study, we found that in contrast, it is retained in the great majority of composite rhabdoid tumors, including those arising within neoplasms that also commonly harbor 22q deletions, such as meningiomas. The latter is particularly relevant given that *INI1* mutations have been recently reported in a small subset of meningiomas.[37,38] Given that this gene was not inactivated in our cases, it is likely that the primary target in the subset of rhabdoid meningiomas with 22q deletion is the more telomeric *NF2* gene on 22q12, just as it is in classic meningiomas.

Recent immunohistochemical studies of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors have shown that there was uniform loss of INI1 throughout the entire tumor, both in rhabdoid and nonrhabdoid tumor cells.[23,24] Similarly, composite rhabdoid tumors in the current study tended to retain expression throughout the tumor, regardless of cytologic features. The cumulative data therefore argue against the notion that there is a common molecular denominator involved in the formation of all rhabdoid cells and provide further support for the existence of both a distinct 'entity' and a secondary 'phenotype'. Nevertheless, the possibility of rare composite rhabdoid tumors with loss of expression is intriguing, as in our case of the retroperitoneal leiomyosarcoma in which nearly the entire tumor was composed of epithelioid and rhabdoid cells and the diagnosis was based on smooth muscle differentiation by electron microscopy. The 29-year-old patient was an unlikely candidate for a diagnosis of malignant rhabdoid tumor, although not impossible, since we and others have encountered rare examples in adult patients.[20,39–50] Lastly, *INI1/hSNF5* mutation analysis was also attempted on this case, but the DNA did not amplify well (data not shown). In a recent study of pediatric CNS tumors, there was one case of an oligodendroglioma with loss of expression and a second case of mixed oligoastrocytoma with focal loss.[23] Similarly, a study of soft-tissue tumors revealed a few examples of synovial and epithelioid sarcomas with either weak or focal immunoreactivity.[24] Therefore, the possibility that INI1 is rarely involved in other tumor types must be considered

and would not be entirely surprising, given that most tumor suppressors are not absolutely specific to any single tumor type. Additional studies are needed to explore this possibility further. In any case, our data strongly argue that in the appropriate context, loss of INI1 expression is diagnostic of malignant rhabdoid tumor or atypical teratoid/rhabdoid tumor.

In summary, INI1 immunohistochemistry represents the most useful ancillary technique currently available for resolving the differential diagnosis of malignant rhabdoid tumor or atypical teratoid/rhabdoid tumor versus composite rhabdoid tumor, given that immunohistochemistry is much more widely available than FISH and both the sensitivity and specificity of this technique are considerably higher. Since neither technique is 100% accurate in all scenarios though, it remains important to consider all the relevant clinical, immunohistochemical, and genetic data (eg FISH, quantitative PCR, mutation analysis, etc) in complex cases.

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