Sellar Atypical Teratoid/Rhabdoid Tumor (AT/RT)

A Clinicopathologically and Genetically Distinct Variant of AT/RT

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Abstract: Atypical teratoid/rhabdoid tumors (AT/RTs) are rare aggressive tumors of the central nervous system that predominantly affect infants. Although adult AT/RT are rare, accumulated cases have revealed adult-specific AT/RT in the sellar region. Twelve previously reported cases of sellar AT/RT exclusively occurred in adult females, suggesting biological differences from conventional infant AT/RT. We herein investigated a series of 6 sellar AT/RT for histopathologic features, the molecular status of the *INI1*/*SMARCB1* gene, and clinical courses. All 6 cases were adult females, ranging in age from 21 to 69 years old. Tumors were histologically characterized by a hemangiopericytoma-like stag-horn vasculature within a dense, diffuse proliferation of jumbled cells and a small number of scattered rhabdoid cells. This vascular pattern is not a common finding in AT/RT and appears to be a characteristic histology of sellar AT/RT. Biallelic alterations in the *INI1* gene were identified by fluorescence in situ hybridization, direct sequencing, and multiple ligation-dependent probe amplification analyses in 4 of the 5 cases analyzed. Three of the 4 cases harbored 2 different mutations, presumably on different alleles (compound heterozygous mutations), and 1 case of which had a splice-site mutation. Combined with previous findings, the prevalence of compound heterozygous mutations and splice-site mutations was significantly higher in sellar AT/RT than in pediatric AT/RT. Sellar AT/RT represent a clinicopathologically and possibly genetically distinct variant of AT/RT showing a characteristic demography, different patterns of *INI1* alterations, and a histology featured by a unique vasculature.

Key Words: AT/RT, sellar region, *INI1*, stag-horn appearance

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Atypical teratoid/rhabdoid tumors (AT/RTs) are rare aggressive tumors of the central nervous system that predominantly affect children younger than 3 years old.[1] They are histologically characterized by the presence of rhabdoid cells and a jumble of cells with a pale, clear, or vacuolated cytoplasm. Neoplastic cells also demonstrate histologic and immunohistochemical evidence of divergent differentiation along neuroectodermal, mesenchymal, and epithelial lineages.[1,2] In the revised 4th edition of the World Health Organization classification, AT/RT have been molecularly defined by the inactivation of either the *INI1*/*SMARCB1* or *BRG1*/*SMARCA4* genes; however, most cases harbor the former alterations.[3] Regarding *INI1* alterations, approximately 20% to 25% of cases have homozygous deletions of the *INI1* gene, while most of the other cases have a mutation in 1 allele with the second allele being lost due to a structural deletion in 22q11.2, monosomy 22, or an acquired event of copy number neutral loss of heterozygosity; a different mutation in each allele, a compound heterozygous mutation, is rare.[4,5] Mutation hotspots are exons 5 and 9, with mutations in splice sites being rare, except in familial cases.[4,6,7]

AT/RT rarely occur in adults, with only 64 cases being reported to date.[8–59] Accumulated cases revealed differences in tumor localization from conventional infant cases; adult AT/RT most frequently occur in the cerebral hemisphere, followed by the sellar region, whereas infant AT/RT commonly occur in the posterior fossa, followed by the cerebral hemisphere.[60] Sellar AT/RT were initially described by Kuge et al in 2000[15] and 12 cases have since been reported.[15,23,30,35,36,43,45,47,52,56] Sellar AT/RT exclusively occur in adult females and have never been reported in the typical

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age group of pediatric patients, suggesting biological differences from conventional AT/RT. However, each of the previous reports only documented 1 or 2 cases, and, thus, the characteristics of this tumor have not yet been elucidated in detail. Although biallelic alterations in the *INI1* gene have been identified in only 3 of the 12 cases at the DNA level, this finding is of importance; 2 of the 3 cases harbored 1 coding-sequence mutation and 1 splice-site mutation, presumably on different alleles of the *INI1* gene.[23,52,56]

Regarding histology, the hemangiopericytoma-like "stag-horn" vasculature that featured in our previous case of sellar AT/RT[56] is not a general finding of AT/RT, and we were unable to find any reported cases with these vessels described. However, the existence of a similar vascular pattern may be inferred from the figure of another sellar AT/RT,[35] suggesting that this vascular pattern is a common histologic feature of sellar AT/RT, but has not been focused on in other sellar cases.

We herein investigated a series of 6 sellar AT/RT for histopathologic features, the molecular status of the *INI1* gene, and clinical courses to clarify in more detail the clinicopathologic and genetic outlines of this rare tumor.

MATERIALS AND METHODS

Tumor Samples

Six cases of sellar AT/RT were collected for this study (Table 1). Two cases were from the consultation files of 1 of the authors (T.H.). Four cases were previously reported.[15,30,47,56] Sections for genetic analyses and immunohistochemistry were prepared from formalin-fixed paraffin-embedded (FFPE) tissue specimens. The study protocol was approved by the Ethics Committee of Gunma University.

Immunohistochemistry

Eight primary antibodies directed against the following antigens were applied for all cases: INI1 (BAF47, 1:100; BD Biosciences, San Jose, CA), epithelial membrane antigen (E29, 1:100; Dako, Glostrup, Denmark), α-smooth muscle actin (1A4, 1:3,200; BioMakor, Rehovot, Israel), cytokeratin (CAM5.2, 1:5; BD Bioscience), glial fibrillary acidic protein (polyclonal, 1:5000; our own[61]), vimentin (V9, 1:200; Dako), STAT6 (sc-621, 1:200; Santa Cruz Biotechnology, Santa Cruz, CA), and Ki-67 (MIB-1, 1:100; Dako). A commercially available biotin-streptavidin immunoperoxidase kit (Histofine, Nichirei, Tokyo, Japan) and diaminobenzidine were used for coloration.

The staining intensity of each antibody, except for INI1, STAT6, and Ki-67, was evaluated as a ratio (%) of positive tumor cells relative to the total number of tumor cells and scored as follows: −, totally negative; 1+, few tumor cells (< 10%) are positive; 2+, scattered tumor cells (10% to 50%) are positive; 3+, diffusely (> 50% of tumor cells) positive.

Fluorescence In Situ Hybridization Analysis

Dual-probe hybridization using an intermittent microwave irradiation method was applied to 4-μm-thick FFPE tissue sections, as described previously.[62] A fluorescence in situ hybridization (FISH) probe encompassing the *INI1* gene at 22q11.2 was prepared from the bacterial artificial chromosome clone, RP11-71G19, and a reference probe located at 22q13.32 was from RP11-262A13, labeled with ENZO orange-dUTP and ENZO green-dUTP, respectively.[63] Metaphase FISH to verify clone mapping positions was performed using the peripheral blood cell cultures of a healthy donor.

Direct DNA Sequencing for the *INI1* Mutation

Genomic DNA was extracted from FFPE sections as previously described,[63] and was amplified and sequenced using primers for exons 1 to 9 of the *INI1* gene.[63]

Multiplex Ligation-dependent Probe Amplification Analysis

Copy number changes (deletions or duplications) in exons of the *INI1* gene and flanking genes were analyzed by an multiplex ligation-dependent probe amplification (MLPA) analysis. The SMARCB1 MLPA test kit P258-C1 (MRC-Holland, Amsterdam, the Netherlands) was used, and electrophoresis data were analyzed using Gene Mapper software (Life Technologies, Carlsbad, CA) and normalized by Coffalyzer.net software (MRC-Holland). A dosage quotient (probe ratio) of between 0.3 and 0.7 was taken to be indicative of a heterozygous deletion,[64] whereas a value < 0.2 was taken to represent a homozygous deletion.

Statistical Analysis

Categorical variables were compared using the Fisher exact test. A survival analysis was performed using the Kaplan-Meier estimation for survival curves and the log-rank test using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (version 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria).[65] Overall survival (OS) time was defined as the time from the date of diagnosis to the date of death. In all analyses, $P < 0.05$ was considered to be significant.

RESULTS

Clinical Data

All 6 cases were adult female patients (Table 1). The age at diagnosis ranged between 21 and 69 years. Surgical resection was performed in all cases. After surgery, case 2 received radiation therapy alone, whereas the other 5 cases received concomitant chemoradiotherapy; cases 1, 3, 4, and 5 received multiagent chemotherapy including cisplatin and etoposide; case 6 received temozolomide alone. Five patients died of the disease within 3 years and 1 patient (case 6) remains alive 37 months after the diagnosis; median OS estimated by the Kaplan-Meier method was 30.5 months.

Histopathologic Findings

All tumors were entirely or mostly composed of a dense, diffuse proliferation of medium to small-sized cells with vesicular nuclei that had prominent nucleoli (Figs. 1A–F). The variability of the cytoplasmic features of tumor cells—

scant, eosinophilic, pale, clear, or vacuolated—created a jumbled appearance. A small number of rhabdoid cells that had an eosinophilic cytoplasm with hyaline inclusions, discrete cell borders, and eccentric nuclei were observed in a scattered manner (Fig. 1E). Frequent mitotic and apoptotic figures were detected. Cases 3 and 5 contained components of spindle cells; a relatively looser appearance textured by short spindle cells was observed in case 3 (Fig. 1C), and a tightly packed fascicular architecture was noted in case 5 (Fig. 1G).

Thin-walled branching hemangiopericytoma-like vessels, the so-called stag-horn vasculature, were observed in all 6 cases (Figs. 1A–F); the vascular pattern was observed throughout specimens from cases 1, 2, 4, and 6, and was partially observed in cases 3 and 5. In addition, capillaries in the adjacent normal anterior pituitary glands with the invasion of isolated and scattered tumor cells also dilated and created a similar appearance in cases 2, 4, and 5 (Fig. 1H).

Immunohistochemistry revealed that tumor cells were negative for INI1, whereas endothelial cells were immunoreactive as an internal control (Fig. 2A). Polyphenotypic immunoreactivities, a characteristic feature of AT/RT,[2] were confirmed in all cases (Table 1). Vimentin was positive with diffuse or scattered cytoplasmic staining in all cases (Fig. 2B). Epithelial membrane antigen was positive in rare or scattered tumor cells with strong surface reactivity in cases 1, 2, 3, and 5 (Fig. 2C). Cases 1 and 6 were positive for CAM5.2 (Fig. 2D) and only case 4 was positive for glial fibrillary acidic protein (Fig. 2E). α-smooth muscle actin was positive in all cases, with diffuse and strong positivity in case 5 only (Fig. 2F). STAT6 was negative in all 6 cases. MIB-1 labeling indices were consistently high, ranging between 26% and 85%.

FISH Analysis, Direct DNA Sequencing for the *INI1* Mutation, and MLPA Analysis

A FISH analysis and direct sequencing were performed in 5 cases, except for case 1 (Table 1). The results of the FISH analysis did not show the loss of chromosome 22q containing the region of the *INI1* gene, in any of the 5 cases. Direct sequencing revealed that 3 of the 5 cases harbored compound heterozygous mutations; in case 2, 1 was c.370_371delA in exon 4 and the other was c.528_529delC in exon 5; in case 4, 1 was the c.544C > T mutation in exon 5 and the other was c.681_696/685_700del16 in exon 6 (Fig. 3); in case 6, 1 was c.150_151insC in exon 2, and the other was c.795 + 1delG in the donor splice site of intron 6, as previously reported.[56] We performed an MLPA analysis on 2 cases, in which biallelic *INI1* alterations were not confirmed by FISH and direct sequencing, and found homozygous deletions in exons 1 to 5 in case 3, whereas no copy number change was detected in case 5.

DISCUSSION

The demographic characteristic, the most distinctive feature of sellar AT/RT, was validated in and supported by this study; all 14 sellar AT/RT, combining 6 cases in our cohort and remaining 8 cases from the literature, exclusively occurred in adult females. In contrast, pediatric AT/RT and adult AT/RT at sites other than the sellar region showed a slightly stronger male predominance (Table S1, Supplemental Digital Content 1, http://links.lww.com/PAS/A500). Although not exclusively, some tumors in non–sex-related organs show marked sex differences in their development; mucinous cystic neoplasms (MCN) of the pancreas (> 95%), retroperitoneum (90%), and mesentery (90%), mixed epithelial stromal tumor of the kidney (> 85%), solid-pseudopapillary neoplasms of the pancreas (> 90%), and lymphangioleiomyomatosis in the lung (> 99%) predominantly affect female patients. The underlying mechanisms of this female predominance have not yet been elucidated; however, cells incorporated from the primitive ovary may give rise to MCN, and expression of hormone receptors may be related to proliferation of MCN and lymphangioleiomyomatosis.[66–72] The ages of patients of sellar AT/RT were evenly distributed from 20 to 69 years old, that is, no deviation toward young adults or the elderly was found, and the occurrence did not appear to be related to hormonal profiles, unlike other female-specific cancers such as breast and endometrial cancers.[73,74] Other biological differences from conventional AT/RT, on genetic and epigenetic levels, seem to exist.

In the present study, we investigated the genetic status of the *INI1* gene in 5 cases of sellar AT/RT, and biallelic alterations in the gene were identified in 4 cases. Three of 5 cases in this study, and 4 of 7 cases (57%)

TABLE 1. Case List With Clinical, Histologic, and Cytogenetic Features

			Immunohistochemistry						
Case	Age (y)/Sex	Stag-horn Vasculature	INI1	Vimentin	EMA	CAM 5.2	GFAP	α-SMA	MIB-1 LI
1[15]	31/F	Present	–	2+	1+	2+	–	1+	NA
2[30]	56/F	Present	–	3+	1+	–	–	2+	30%
3[47]	44/F	Present (partial)	–	3+	2+	NA	–	1+	85%
4	26/F	Present	–	3+	–	–	2+	1+	30%
5	21/F	Present (partial)	–	3+	1+	–	–	3+	26%
6[56]	69/F	Present	–	2+	–	1+	–	2+	60%

The frequency of immunopositive tumor cells was semiquantitatively assessed (ie, –: absent; 1+: rare; 2+: scattered; 3+: diffuse).

CDDP indicates cisplatin; CNA, copy number aberration; EMA, epithelial membrane antigen; F, female; GFAP, glial fibrillary acidic protein; IT, intrathecal injection; IFM, ifosfamide; LI, labeling index; MTX, methotrexate; NA, not assessed; SMA, smooth muscle actin; SRS, stereotactic radiosurgery; VP-16, etoposide.

when combined with those from literature, harbored compound heterozygous mutations. In contrast, only 1 of 116 cases (< 1%) of pediatric AT/RT with detectable biallelic *INI1* alterations harbored this type of mutation[75]; the prevalence of compound heterozygous mutations significantly differed between sellar AT/RT and conventional AT/RT ($P < 0.001$, Fisher exact test). Furthermore, the splice-site mutations previously reported in case 6 and 1 case in the literature were not detected in the 4 other cases examined in the present study; however, their frequency was still significantly higher in sellar AT/RT than in pediatric AT/RT among the same cohort (1.7%, $P = 0.012$, Fisher exact test).[75] Homozygous deletions of the whole *INI1* gene, which is a common type of *INI1* alteration in conventional AT/RT,[4] were not observed in our 5 cases (Table 1) or in cases from the literature (Table 2). These differences in the type of *INI1* alteration are noteworthy, considering the similar discrepancies observed between AT/RT and *INI1*-deficient renal/extrarenal RTs; approximately 25% of AT/RT, 40% of renal RT, and 70% of extrarenal RT have homozygous deletions of the whole *INI1* gene, and mutational hotspots in the *INI1* gene are exons 5 and 9 among AT/RT and exon 2 among renal RT.[4]

Regarding histology, all 6 sellar AT/RT in this study showed the hemangiopericytoma-like stag-horn vasculature within a dense, diffuse proliferation of jumbled cells and rare rhabdoid cells (Figs. 1A–F). This vascular pattern is not a general finding of AT/RT, suggesting that the vasculature is a distinct histologic feature of sellar AT/RT. We also reviewed the literature for other sellar tumors, such as pituitary adenoma, pituicytoma, and spindle cell oncocytoma, but found no descriptions of a similar vasculature.[76–78] Given the observation that similar appearances were created by dilated capillaries in adjacent anterior pituitary glands with minimal tumor invasion (Fig. 1H), it can be inferred that stag-horn vasculature in sellar AT/RT may be associated with the nature of capillaries in normal anterior pituitary glands, which may resemble this feature with increased blood flow to the aggressive tumor.

Adult AT/RT have been reported to follow a longer course than pediatric AT/RT; however, statistical analyses were not performed in previous studies.[29,37,55] The median OS of sellar AT/RT in the present study was 30.5 months (range, 17 to 37 mo), which seems to represent a more favorable outcome than that for conventional AT/RT cases, the median OS of which was reported to be 11.1 to 14.3 months.[79,80] Although direct comparisons may be biased due to limitations such as heterogeneity in treatments and the small number of sellar AT/RT cases, we compared median OS among 3 groups: 12 cases of sellar AT/RT (6 cases in our cohort and 6 cases from the literature), 47 cases of adult AT/RT occurring in sites other than the sellar region (Table S2, Supplemental Digital Content 2, http://links.lww.com/PAS/A501), and 125 cases of pediatric AT/RT in a recent large study with available individual follow-up data.[81] The median OS for each group was 30.0 months (95% confidence interval [CI], 9-35 mo), 20.0 months (95% CI, 13-30 mo), and 12.9 months (95% CI, 10.2-16 mo), respectively (Fig. S1, Supplemental Digital Content 3, http://links.lww.com/PAS/A502). No significant difference existed between sellar AT/RT and pediatric AT/RT ($P = 0.231$, log-rank test) or between sellar AT/RT and other adult AT/RT ($P = 0.747$, log-rank test), and this may have been due to insufficient sample numbers of sellar AT/RT. We also compared all 59 reported cases of adult AT/RT with the above 125 cases of pediatric AT/RT, and found a tendency toward better median OS in adult AT/RT (24.0 mo; 95% CI, 18-30 mo) than in pediatric AT/RT ($P = 0.071$, log-rank test).

Two recent landmark studies by Johann et al[82] and Torchia et al[75] both showed that AT/RT are a heterogenous disease comprised 3 different molecular subgroups characterized by distinct methylome profiles, enhancer landscapes, and subgroup-specific regulatory networks. These classi-

TABLE 1. *(Continued)*

Genetic Analysis					
***INI1* Exon Sequencing**	**FISH for 22q11.2/ 22q13**	**MLPA**	**Radiation**	**Chemotherapy**	**Clinical Outcomes**
NA	NA	NA	Local, posterior fossa	1st: CDDP + VP-16, 2nd: MTX (IT)	Dead, 28 mo
Exon 4; c.370_371delA; frame shift Exon 5; c.528_529delC; frame shift	2/2 copies	NA	SRS, local, spine	No	Dead, 23 mo
No mutation	2/2 copies	Homozygous exon 1-5 deletions	Yes (no detail)	IFM + CDDP + VP-16	Dead, 17 mo
Exon 5; c.544C > T; nonsense Exon 6; c.681_697del; frame shift	2/2 copies	NA	Local, spine	1st: MTX (IT), 2nd: IFM + CDDP + VP-16	Dead, 33 mo
No mutation	2/2 copies	No CNA	Local	IFM + CDDP + VP-16	Dead, 35 mo
Exon 2; c.150_151insC; frame shift Intron 6; c.795 + 1delG; splice site	2/2 copies	NA	Local	Temozolomide	Alive at 37 mo

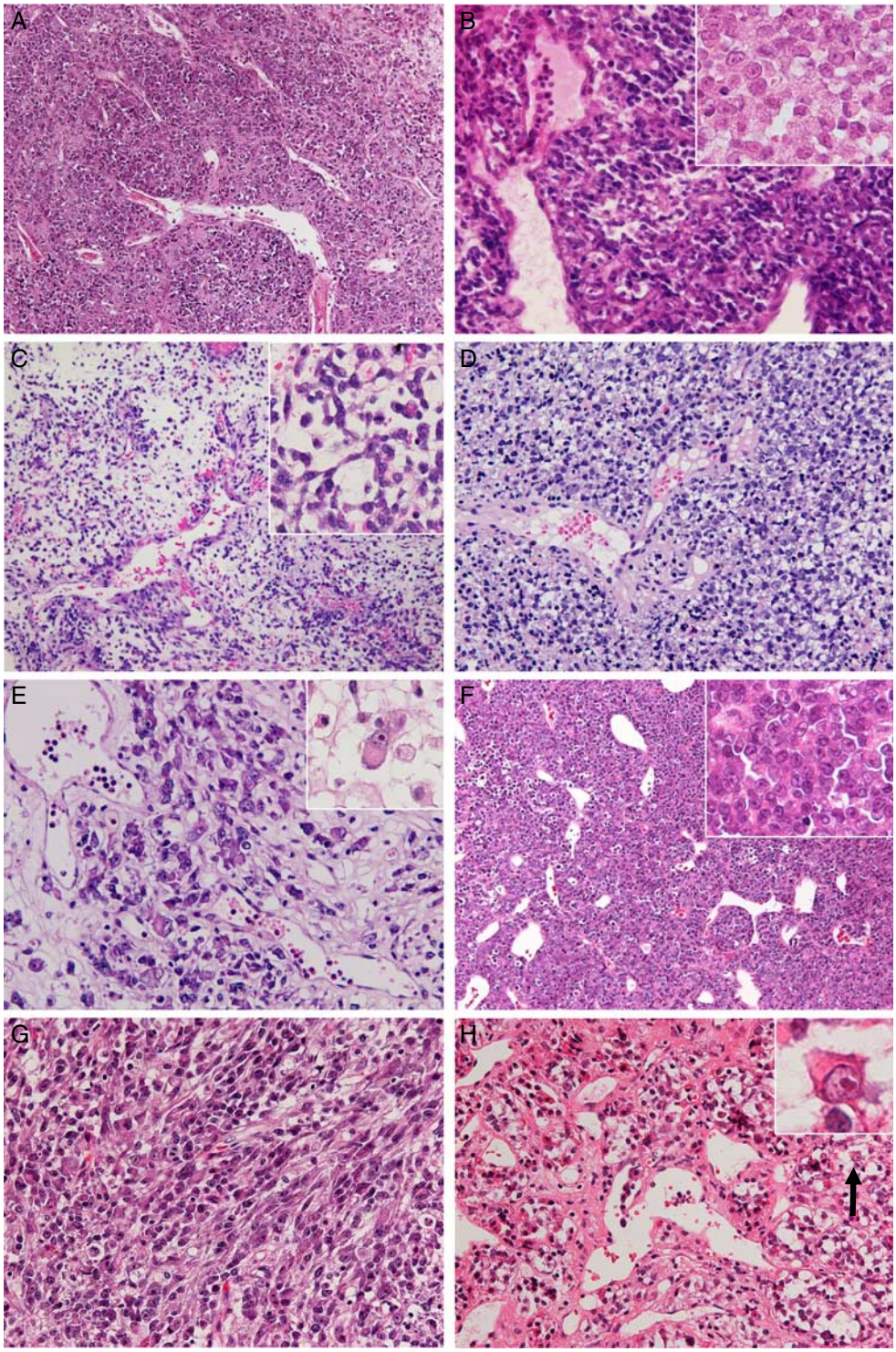

FIGURE 1. Microscopic appearance of sellar AT/RTs (A–F; cases 1–6, respectively, G; case 5) and an adjacent normal anterior pituitary gland (H; case 5). All tumors are entirely or mostly composed of a dense, diffuse proliferation of medium to small-sized cells (A–F). The insets in (B) and (F) are the magnified images. In minor parts of tumors, a relatively looser appearance textured by short spindle cells (C inset) and a tightly packed fascicular architecture (G) are observed. Rare rhabdoid cells displaying an eosinophilic cytoplasm with hyaline inclusions, discrete cell borders, and eccentric nuclei are noted (E inset). The thin-walled branching "stag-horn vasculature" is observed in all 6 cases (A–F). Capillaries in the adjacent normal anterior pituitary gland with the invasion of scattered tumor cells (arrow and H inset) also dilate and create a similar stag-horn appearance (H).

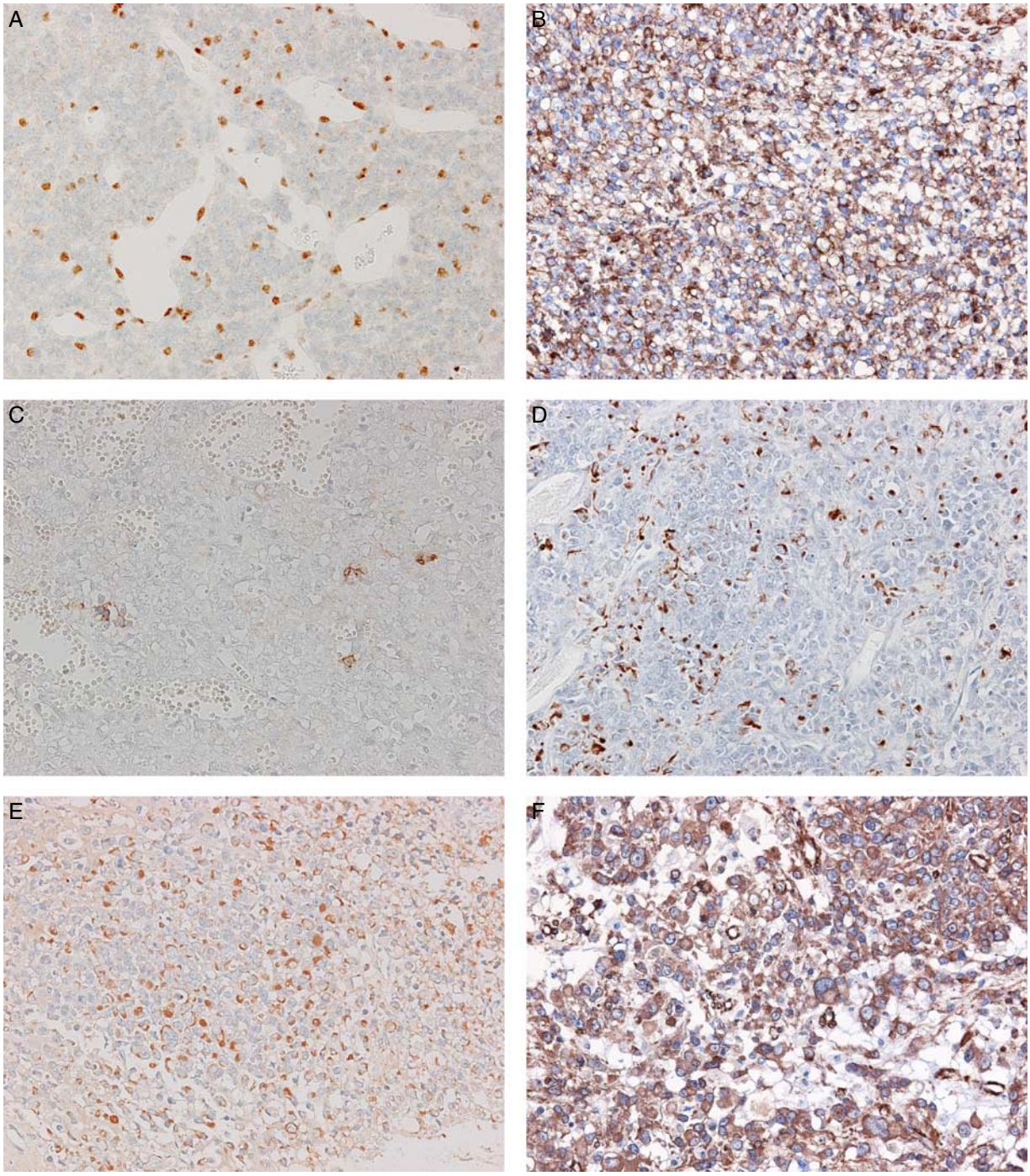

FIGURE 2. Immunohistochemistry. Tumor cells are negative for INI1, whereas endothelial cells are positive as an internal control (A; case 6). Vimentin is positive as diffuse (>50%) cytoplasmic staining in case 3 (B). Epithelial membrane antigen is positive in a limited number of tumor cells (<10%) in case 1 with strong surface reactivity (C). Scattered tumor cells (10% to 50%) are positive for CAM5.2 (D) and the glial fibrillary acidic protein (E) in cases 1 and 4, respectively. α-smooth muscle actin is positive in all cases with diffuse strong positivity in case 5 (F).

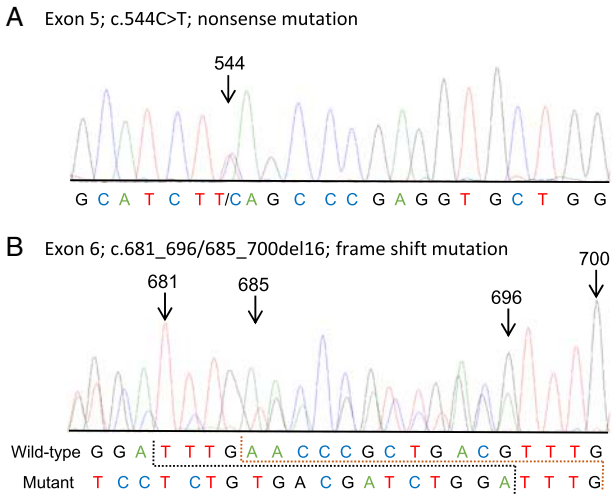

FIGURE 3. Illustration of compound heterozygous mutations. Two different *INI1* mutations observed in case 4 are shown; one was the c.544C>T nonsense mutation in exon 5 (A), and the other was the c.681_696/685_700del16 frame shift mutation in exon 6 (B).

fications were also associated with demographic features (patient age), the tumor location (supratentorial or infratentorial), and type of *INI1* alteration (focal alterations or broad deletions). However, these cohorts (except for 1 adult case in the latter study) mostly consisted of pediatric cases and sellar cases were not included. In the present study, sellar AT/RT showed distinct features in terms of demography, tumor location, the type of *INI1* alteration, and histologic features; these differences from conventional AT/RT seem to be more remarkable than those observed among the molecular subgroups in the above studies. Nevertheless, it currently remains unclear whether a methylome analysis has the ability to separate sellar AT/RT from other molecular subgroups based on recent findings showing that 10 cases of cribriform neuroepithelial tumors (CRINET), rare nonrhabdoid brain tumors showing a cribriform growth pattern and *INI1* inactivation with favorable long-term outcomes, exclusively clustered within one of these AT/RT subgroups in a methylome analysis.[83]

In conclusion, sellar AT/RT represent a clinicopathologically—and possibly genetically—distinct variant of AT/RT showing a characteristic demography, different

TABLE 2. Literature Review of Sellar AT/RTs

References	Age (y)/ Sex	INI1 IHC	Genetic Analysis: *INI1* Exon Sequencing	Genetic Analysis: FISH for 22q11.2	Radiation	Chemotherapy	Clinical Outcomes
Raisanen et al[23]	20/F	—	Exon 2; c.118delC; frame shift	Heterozygous deletion	Yes (no detail)	Yes (no detail)	Alive at 28 mo
Raisanen et al[23]	31/F	—	ND	Heterozygous deletion	Yes (no detail)	ND	Dead, 9 mo
Las Heras and Pritzker[35]	46/F	—	ND	ND	ND	ND	ND
Schneiderhan et al[36]	61/F	—	ND	ND	ND	ND	Dead, 3 mo*
Schneiderhan et al[36]	57/F	—	ND	ND	Yes (no detail)	ADM + CDDP	Alive at 6 mo
Moretti et al[43]	60/F	—	ND	Heterozygous deletion	Local	1st:ADM + VNB 2nd:CBDCA	Dead, 30 mo
Park et al[45]	42/F	—	ND	ND	Craniospinal	Multiagent†	Alive at 24 mo
Biswas et al[52]	48/F	—	Exon 2; c.146C > G; nonsense Intron 5; c.629 + 2T > G; splice site	ND	No	VCR + ADM + CPA, IFM + CBDCA + VP-16	ND

*Died 3 months after the second operation.
†Consisted of VCR, CDDP, ADM, and VP-16/IFM alternating with VCR, VP-16, IFM, and CBDCA.
ADM indicates adriamycin; CBDCA, carboplatin; CPA, cyclophosphamide; IFM, ifosfamide; IHC, immunohistochemistry; ND, not determined; VCR, vincristine; VNB, vinorelbine ditartate.

patterns of *INI1* alterations, and a histology featured by a unique vasculature. Further studies of more cases with comprehensive (epi)genome-wide analyses are needed to confirm that sellar AT/RT are a molecularly distinct variant of AT/RT.

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