Atypical Teratoid/Rhabdoid Tumors and Choroid Plexus Tumors: When Genetics "Surprise" Pathology

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Atypical teratoid/rhabdoid tumor (ATRT) and choroid plexus tumors (CPT) represent, so far, 2 well defined types of CNS neoplasm on the basis of their histological features and clinical presentation (10). While CPTs are intraventricular epithelial tumors arising from choroid plexus epithelium, the cellular origin of ATRTs is still unknown. Inactivating mutations of the *hSNF5/INI-1* gene located in the chromosomal region 22q11.2 are regarded as a crucial step in the molecular pathogenesis of ATRTs; the genetic changes associated with CPTs are largely unknown. However, the recent finding of inactivation of *hSNF5/INI-1* in choroid plexus carcinomas and papillomas (9, 18) points to a closer relationship between these 2 entities. This is supported by the occurence of choroid plexus carcinomas (CPC) in the setting of families with rhabdoid predisposition syndrome (RPS), (19) caused by germ line inactivation of the *INI1* gene.

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Atypical teratoid/rhabdoid tumors mainly affect young children under the age of 3 years; congenital cases have occasionally been reported. Their biological characteristics and some of their histological features are similar to those of malignant rhabdoid tumors of the kidney. ATRTs occur in the posterior fossa in 52% of the cases, frequently involving the cerebello-pontine angle. Forty percent of the cases are supratentorial hemispheric tumors, less frequent are pineal or spinal locations. One third of tumors are disseminated at the time of diagnosis (10).

ATRTs are characterized histologically by the presence of rhabdoid cells, ie, cells with eccentric nuclei with prominent single large nucleoli and prominent cytoplasm with abundant fibrillary inclusions. Such cells, which stain strongly for the intermediate filament vimentin, can be observed in variable amounts throughout the tumor. Usually, additional cellular components are present representing different lines of differentiation, including primitive neuroectodermal, glial, epithelial, and mesenchymal cells. These components can cause diagnostic problems, so that some ATRTs may be misdiagnosed as PNETs/medulloblastomas, glioblastomas, choroid plexus carcinomas or malignant teratomas. The immunophenotype of ATRTs reflects their cellular heterogeneity. In addition to vimentin and epithelial membrane antigen (EMA), which is present in most tumor cells, smooth muscle actin (SMA), cytokeratins, GFAP, and synaptophysin can be detected in variable amounts (6, 10, 16).

Clinically these tumors behave very aggressively. Therapeutic approaches are mainly based on surgical resection and adjuvant high-dose chemotherapy; radiotherapeutic treatment regimens are not widely accepted because of the young age of the majority of the patients. An initial response to such regimens can be observed in approximately 50% of cases. However, the tumors usually quickly recur and the overall survival, at two years of follow-up, is less than 20% (10).

ATRTs, as well as their extracerebral counterparts in the kidney, are genetically characterized by monosomy of chromosome 22 or partial deletion of 22q11.2 (4). This region contains the *INI1/hSNF5* gene which encodes a component of the SWI/SNF chromatin remodelling complex (3, 5). The gene is inactivated by truncating mutations or by partial or total deletion of the gene. Inactivating mutations of the *hSNF5/INI-1* gene or absence of its RNA and protein (in the absence of genomic alterations) are present in approximately 85% of the cases (3). The Ini-1 protein is a component of the SWI /SNF complex, interacting with sequence specific DNA binding proteins such as c-Myc, EBNA-2 and GADD34 (3). It has been hypothesized that Ini-1 can modify by this mechanism the transcription of many cellular gene implicated in tumorigenesis. The spectrum of specific target genes of *hSNF5/INI-1* is, so far, unknown. Targeted deletion of the *INI-1* gene causes rhabdoid tumors in a subgroup of mice, which clearly

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Authors	Year	N° of cases	Number of cases with INI-1 inactivation	Histological diagnoses	% cases of CPC with INI-1 inactivation
Sevenet et al (1)	1999	12	5	4 CPC, 1 ACPP	66
Chen et al (2)	2001	8	4	4 CPC	50
Weber et al (3)	2001	1	1	1 CPC	100
Gessi et al (4)	2002	29	7	4 CPC, 2 CPP, 1ACPP	40

Table 1. Summary of sporadic choroid plexus tumors carrying *hSNF5/INI-1* mutations. CPC = choroid plexus carcinoma, CPP = choroid plexus papilloma, ACPP = atypical choroid plexus papilloma.
(1) *Human Molecular Genetics* (1999), 8:2359-68.
(2) *Proceedings of American Association for Cancer Research* (2001), 42:860.
(3) *Acta Neuropathologica* (2001), 101:479-82.
(4) *Proceedings of American Association for Cancer Research* (2002), 43:1138.

demonstrates its crucial role in the pathogenesis of rhabdoid tumors (15).

In humans, germline inactivation of the *hSNF5/INI-1* gene causes, in children, multiple rhabdoid neoplasms including cerebral ATRTs (17, 19, 20). Predisposition to the development of cerebral and extracerebral rhabdoid tumors indicates that *INI-1* acts as a tumor suppressor gene, following Knudson's 2-hit model. Sevenet et al (19) therefore proposed the designation of *rhabdoid predisposition syndrome* (*RPS*). However, in such families other brain tumor entities have been diagnosed, including medulloblastomas and choroid plexus carcinomas (19, 20).

Choroid plexus tumors (CPTs) are neoplasms believed to arise from the epithelium of choroid plexus or its specific progenitor cells. They occur at all ages, but are the most common neoplasms in the first year of life and one of the more common during childhood. Congenital cases can also rarely occur. They arise in the ventricular system, where choroid plexus epithelium normally occurs. Overall, the lateral ventricles are affected in 50% of cases, the fourth ventricle in 40% of cases, and the third ventricle in 5% of cases. In comparison to ATRT, a primary location in the cerebellopontine angle is less frequent (10). CPTs represent a spectrum of neoplasms ranging from well differentiated lesions, named papillomas (WHO grade I), to highly aggressive epithelial neoplasm, defined as carcinoma (WHO grade III), with rare intermediate forms (atypical choroid plexus papillomas) whose biological behaviour is not yet defined (10). Choroid plexus carcinomas (CPCs), which occur more frequently in children than in adults, show an aggressive infiltrative growth pattern, and may metastize along CSF pathways and also systemically. Interestingly, even choroid plexus papillomas (CPPs) can seed cells into the CSF.

The clinical behaviour of CPT varies widely but the prognosis is usually good in resectable choroid plexus papillomas. Some of the more aggressive carcinomas can be successfully treated by surgery, radiotherapy and chemotherapy with overall survival of 40% at 5 years (13).

Choroid plexus papillomas are formed by delicate papillae with fibrovascular stroma covered by a single layer of uniform cuboidal cells. Various forms of metaplasia can be found. Mitoses are very rare or absent (10). The presence of frank features of anaplasia, such as cellular pleomorphism, mitoses, necrosis, solid growth pattern and invasion into the surrounding brain parenchyma characterizes CPC. Almost all CPT showsimmunohistochemical staining for vimentin, cytokeratins and a variable staining for S-100 protein and transthyretin (prealbumin). Some cases may show GFAP immunoreactivity (10).

ATRT represents one of the most aggressive tumors in the pediatric age group with poor prognosis; in the last few years, there has been no improvement in overall survival with this tumor despite more aggressive therapeutic regimens. In contrast, the clinical behaviour of CPC is more favourable, at least in a subgroup of patients (13). Therefore, the correct neuropathological differential diagnosis between ATRT and CPC is also of prognostic relevance. In the majority of cases the correct diagnosis can be made on the basis of the presence of rhabdoid cells or non-epithelial components in ATRT; however, in rare cases, expecially in small biopsies, these 2 tumors can show a similar histological and immunophenotypic appearance.

The pathogenesis of choroid plexus tumors is largely unknown. In choroid plexus tumors, DNA sequences of the SV40 papovavirus have been detected, suggesting a possible role of this small primate DNA virus in the evo-

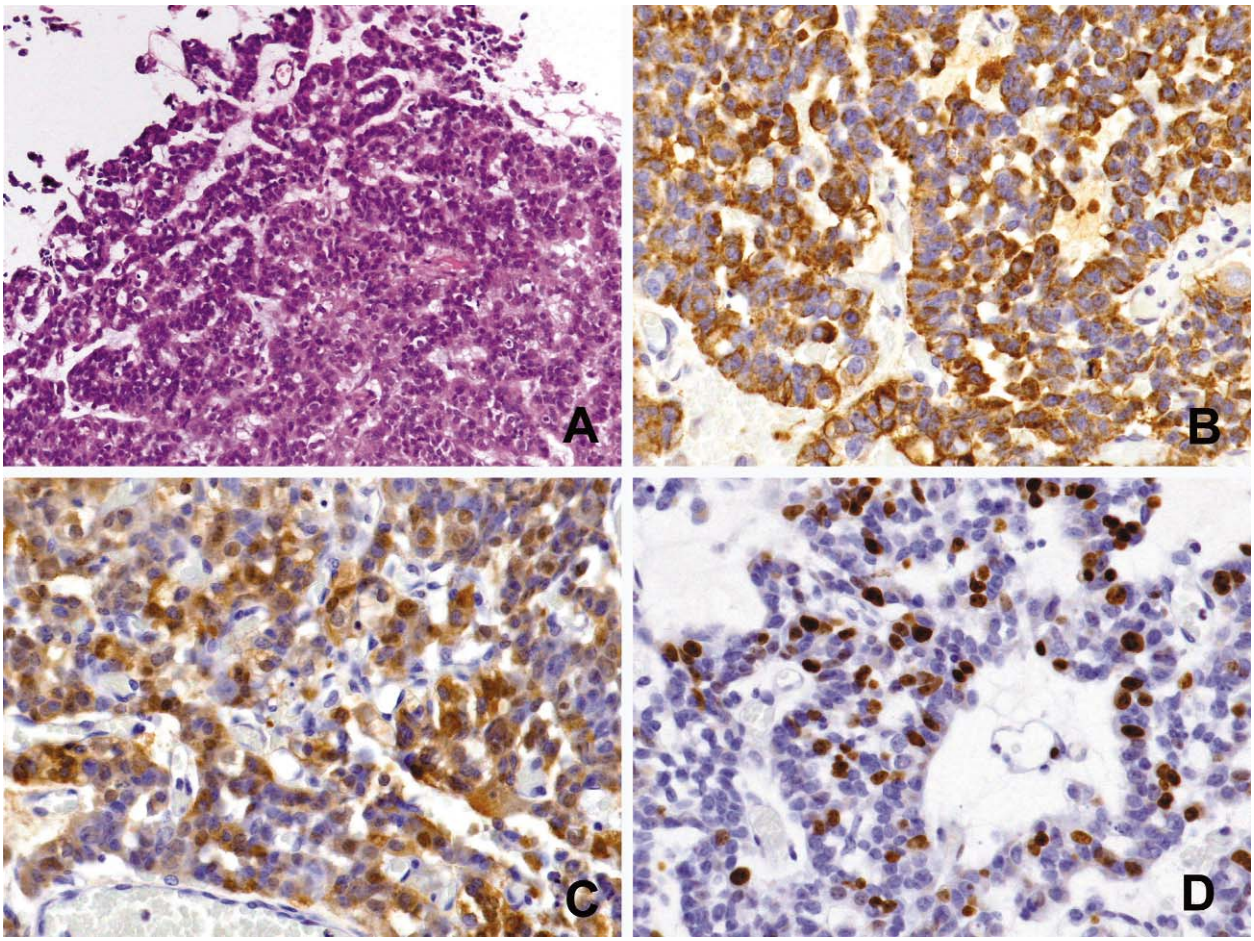

Figure 1. Histological and immunohistochemical features of a choroid plexus carcinoma of the fourth ventricle from a 10-year-old girl. **A.** H&E staining showing papillary and solid histoarchitectures; **B.** cytokeratin expression; **C.** S-100 protein expression; **D.** MIB-1 staining.

lution of CPT (1). These viruses contaminated a polio vaccine widely used in the past. In addition, varying amounts of such DNA sequences have been detected in different kinds of tumors and their causative role has not been confirmed by epidemiological studies. On the other hand, SV40 can cause choroid plexus tumors in murine models, suggesting an oncogenic potential.

Cytogenetically, CPT show several chromosomal changes, in term of gain or loss of various chromosomes (8, 14). Recent data on the molecular genetics of CPT have indicated that inactivation of *hSNF5/INI-1* as well as *TP53* are implicated in the biology of these tumors (9, 18).

The involvement of these 2 tumor suppressor genes in the pathogenesis of CPTs finds further support in the occurrence of CPTs in the setting of the 2 familiar cancer syndromes, in which these genes are inactivated by germ line mutations, ie, Li-Fraumeni (*TP53*) and rhab-

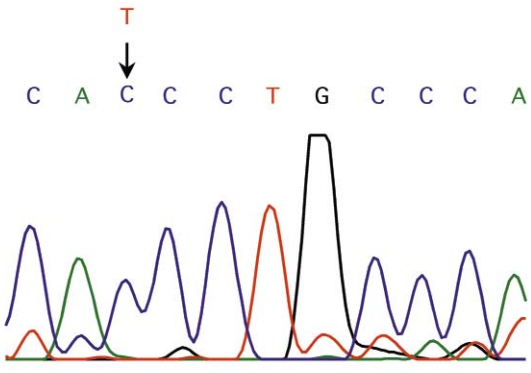

Figure 2. Sequence analysis of the case illustrated in Figure 1. A truncating stop mutation was detected in exon 2 (Arg40stop).

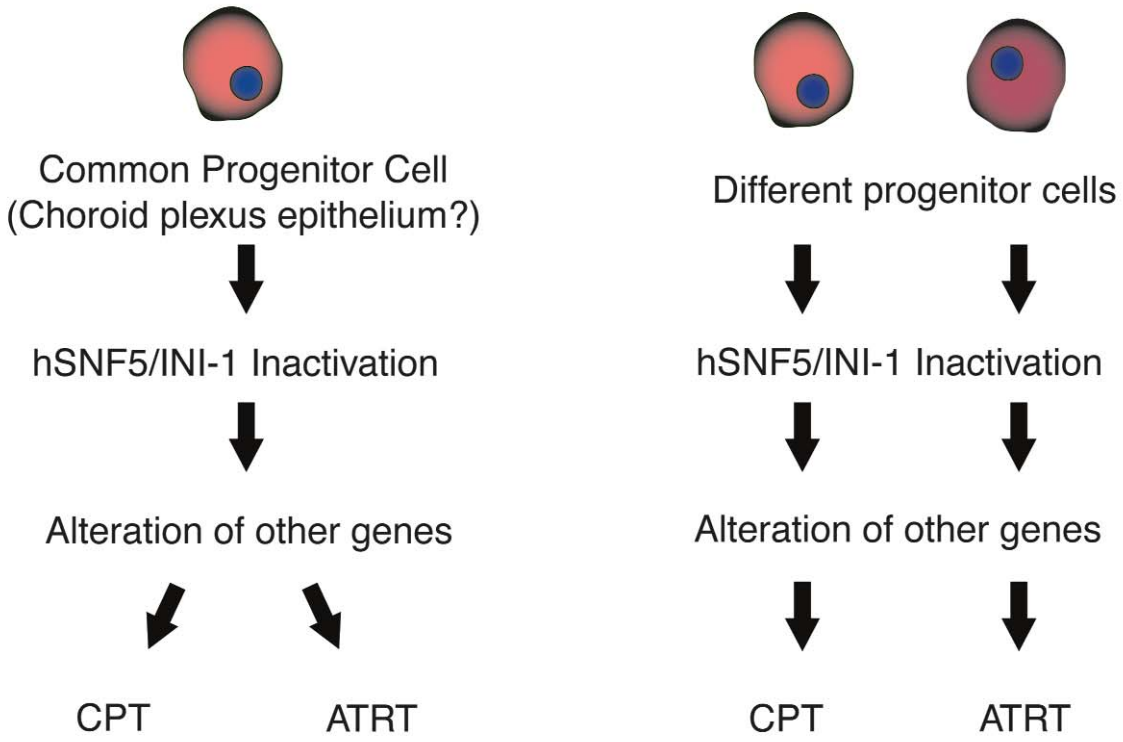

Figure 3. Hypothetical models of the possible relationship of ATRTs and CPTs. They may share a common progenitor cell (left side) or may arise from different progenitor cells affected by *INI-1* mutations (right side).

doid predisposition syndrome (*INI-1*) (11, 19). Such data clearly indicate that the inactivation of *hSNF5/INI-1* gene is not confined to the ATRT but also plays a pivotal role in the oncogenesis of a subset of CPT. Table 1 summarizes the reported series of CPT with *hSNF5/INI-1* inactivation (Table 1). Sevenet et al found alterations (mutation and homozygous deletion) in 66% of CPC examined (18). In a large series of different brain tumor entities, Weber et al found mutation of *hSNF5/INI-1* in the single case of CPC examined (21). Chen et al found mutations in 4 of 8 well documented cases of CPC examined (7). Gessi et al found *hSNF5/INI-1* alteration also in CPP (9). Most of the CPTs analyzed in those series were carcinomas.

What does the finding of *INI-1* mutations—thus far regarded as quite specific for rhabdoid (and ATRT) tumors—in choroid plexus carcinomas mean? Is it possible that these cases had been misdiagnosed and may in fact represent ATRTs with a prominent epithelial component? Location and age show overlapping, though not identical, distributions in ATRT and CPC. In fact, original data suggested the occurence of *INI-1* mutations in medulloblastomas (2), but later it turned out that these cases were most likely misdiagnosed and represented ATRT with prominent PNET-like components. A large series confirmed the absence of *INI-1* mutations in medulloblastomas (12). Might the finding of *INI-1* mutations be a consequence of similar pitfalls?

A strong argument against this possibility is the fact that most of these cases have been intensively characterized, and did not display any of the characteristic cytological or immunocytological features of ATRTs. One of our cases consisting entirely of epithelial cells is shown in Figure 1. This case of an intraventricular tumor displayed a truncating *INI-1* mutation (Figure 2). Chen et al performed additional ultrastructural studies of the tumors and confirmed the nature of the tumor cells (7).

The data on choroid plexus papillomas are more controversial: in fact, only a single series of CPP with inactivation of *hSNF5/INI-1* has been reported (9). However, a recent study, using comparative genomic hybridization (CGH), has shown that loss of chromosome 22q, containing the region of the *hSNF5/INI-1* gene, is present in 47 % of cases (14). These data suggest that inactivation of *hSNF5/INI-1* by mutations or homozygous deletion is present in both CPT as well as in ATRT and extracerebral rhabdoid tumors. The frequency of

hSNF5/INI-1 involvement in CPT, however, is less than 50%, in contrast to ATRT in which such involvement occurs in approximately 90% of cases. This implies that other genes may be involved in the molecular pathogenesis of CPT, or that *INI-1* mutations may be involved in only a subgroup of CPTs.

What is the implication of the presence of *INI-1* mutations in both entities, ATRT and CPT? First, one should be careful in interpreting *INI-1* mutations or chromosome 22 loss as a diagnostic marker because it does not differentiate ATRTs from choroid plexus carcinomas. It may also be possible that other brain tumor entities not yet studied may contain such mutations.

Can we draw any conclusions about the histogenetic origin of ATRTs from these findings? One possibility may be that the same genetic alteration occurs in totally different tumors arising from different progenitor cells. The *TP53* gene, for example, is mutated in gliomas, but also in many other tumor types of different origin. The relative restriction of *INI-1* mutations may also hint at a more provocative hypothesis that ATRTs and CPTs may be derived from similar progenitor cells such as choroid plexus epithelial cells or their specific progenitors. Such a hypothesis may imply that the *hSNF5/INI-1* inactivation is an early common event in the tumorigenesis of both entities. The involvement of other genetic or epigenetic alterations may then explain the different phenotypes and biological behaviour of these tumors (Figure 3). However, the different age-related frequency of location, and the different frequency of *INI-1* mutations argue against this hypothesis if one considers CPTs as a tumor family derived from identical progenitor cells. It may also be a consideration that these two tumors arise from progenitors which are derived from the same lineage but represent different stages of commitment. Following this line, one would suggest that ATRTs may be derived from more immature cells still able to differentiate along in various lineages, and CPTs to be derived from "later" progenitors committed to the (choroid) epithelial lineage.

Further molecular and genetic studies are needed to clarify the patho- and histogenesis of both entities, and their possible molecular relationship.

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