

Case Report

Primary intracerebral INI1-deficient rhabdoid tumor with CD34 immunopositivity in a young adult

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Abstract

Background: Primary CNS malignant rhabdoid tumors are very rare in adults and much less is known about their biological behavior than in children. Recently, two adult cases of SMARCB1 (also known as INI1)-deficient tumor with rhabdoid cells have been described, suggesting an emerging group of primary meningeal SMARCB1-deficient tumors. We have recently encountered a case of INI1-deficient tumor with similar histology and immunophenotype to the above cases, but with a superficial cerebral, yet apparent intra-axial origin.

Case Description: A 22-year-old woman presented with approximately one year history of focal sensorimotor right upper limb seizures and recently developed a slowly progressive weakness in her right hand. An MRI of the brain demonstrated an avidly enhancing lesion centered on the left perirolandic region with no definite dural involvement. The patient underwent a complete surgical excision. Histology revealed a tumor with monotonous epithelioid and spindle-shaped cells in a mucoid/myxoid background. There was focal mitotic activity and a few necrotic areas, in addition to many rhabdoid cells. The immunohistochemistry was negative for INI1 and there was strong positivity with CD34, while focal smooth muscle actin (SMA) and epithelial membrane antigen (EMA) immunoreactivity were also noted.

Conclusions: As an addition to the two cases of adult SMARCB1-deficient tumors recently described, we present a further adult case with a similar immunohistochemical profile but with an apparent intra-axial origin, questioning the necessary meningeal origin of this type of tumor. The prognosis of this adult INI1/SMARCB1-deficient tumor is to be determined, but may be better than the pediatric atypical/teratoid tumor (AT/RT).

Key Words: Atypical teratoid/rhabdoid tumor, CD34, INI1, malignant rhabdoid tumor, SMARCB1

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INTRODUCTION

Atypical teratoid/rhabdoid tumour (AT/RT) is a malignant CNS embryonal tumour composed of poorly differentiated cells with immunohistochemically polyphenotypical differentiation along neuroectodermal, epithelial, and mesenchymal lines frequently containing rhabdoid cells.^[12] The diagnosis of AT/RT requires demonstration of inactivation of SWI/SNF related, matrix-associated, actin-dependent regulator of chromatin, subfamily B member 1 (SMARCB1) or, if intact, SMARCB4 genes, either by immunohistochemistry or by other appropriate molecular techniques. This tumour predominantly affects young children (< age 3) accounting for circa 10% of all CNS tumors in infants. Although the prognosis in children has traditionally been dismal, with few long-term survivors, developments over the last 10 years have, at least for children, been encouraging.^[8] AT/RT is very rare in adults and much less is known about their biological behavior. The reported adult cases tend to occur around the pituitary or less commonly in the hemispheric parenchyma.^[6,10,16]

Recently, Dadone *et al.* described two adult cases of SMARCB1 (also known as INI1, hSNF5, and BAF47)-deficient tumor.^[6] Although those two cases had rhabdoid cells, the phenotype and genotype did not fit diagnostically with entities already known to be SMARCB1-deficient tumors and the authors suggested that they belonged to an emerging group of primary meningeal SMARCB1-deficient tumors. The authors recommended SMARCB1 immunohistochemistry for primary meningeal tumors, which are difficult to classify, especially if immunopositive for EMA and CD34. We have recently encountered a case of INI1 (SMARCB1)-deficient tumor with similar histology and immunophenotype to the above cases, but with a superficial cerebral, yet apparent intra-axial origin.

CASE DESCRIPTION

A 22-year-old woman with no significant medical background presented with approximately one year history of focal sensorimotor right upper limb seizures, characterised by occasional twitching and pins and needles in the right hand and forearm. Over the previous two months she also developed a slowly progressive weakness in her right hand. Seizure activity was well controlled on monotherapy with levetiracetam. An MRI of the brain demonstrated an avidly enhancing lesion centered in the left perirolandic region (involving precentral and postcentral gyri) measuring 38 × 43 × 39 mm [Figure 1a and b]. Multiple serpiginous signal voids were observed in the lesion, but no definite dural involvement, raising the suspicion of an intra-axial tumor. Given the location of the tumor, surgery was performed with the

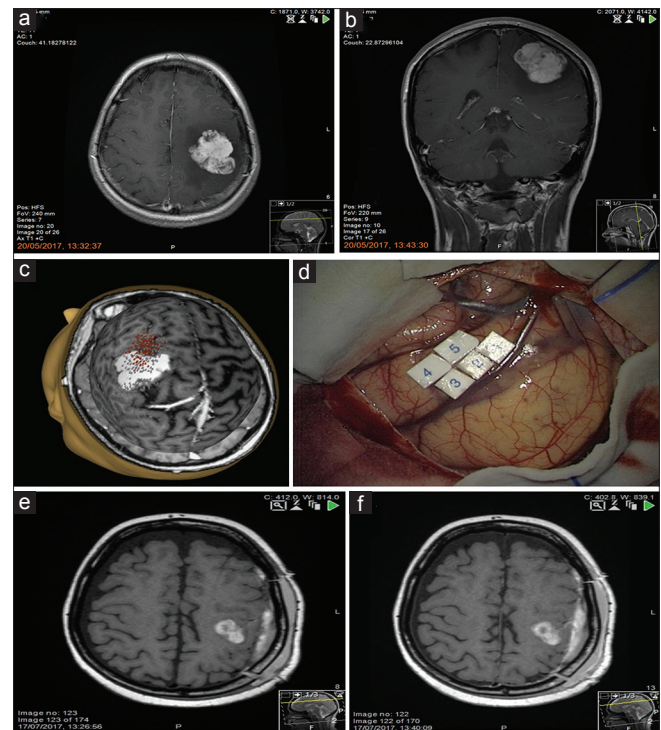


Figure 1: Pre-operative MRI (a, b) T1-weighted post gadolinium images show an avidly enhancing mass with well-defined, lobulated borders in the left frontoparietal region. Preoperative transcranial magnetic stimulation (c) and intraoperative motor mapping and monitoring (d) demonstrate that the primary motor cortex was located in front of the tumor, confirming the location of the tumor within the central sulcus. Post-operative MRI axial T1-weighted pre gadolinium (e) and post gadolinium (f) show a small volume of hemorrhage in the surgical bed but no residual tumor

aid of preoperative transcranial magnetic stimulation and intraoperative motor mapping (monopolar stimulation, “train of 5 technique”).^[2] Both methods demonstrated that the primary motor cortex was located in front of the tumor, therefore confirming the location of the tumor within the central sulcus [Figure 1c and d]. Gross total resection of the tumor was achieved with preservation of the motor mapping throughout the procedure [Figure 1e and f].

The toluidine blue stained intraoperative smear preparation confirmed neoplastic tissue with a loose matrix and monomorphic tumor cells together with associated mast cells but no definite diagnosis could be given [Figure 2a]. Histology showed a tumor composed of cells both epithelioid and spindle-shaped with oval, relatively monotonous, sometimes eccentric, nuclei and prominent nucleoli [Figure 2b-c]. The cytoplasm was frequently vacuolated and also there were many eosinophilic cytoplasmic inclusions in keeping with rhabdoid cells [Figure 2d]. The background matrix was a combination of mucoid/myxoid areas and more hyalinised elements. Although there was some infiltration into surrounding cerebral tissue noted, for the most part the neoplasm was well demarcated from surrounding brain.

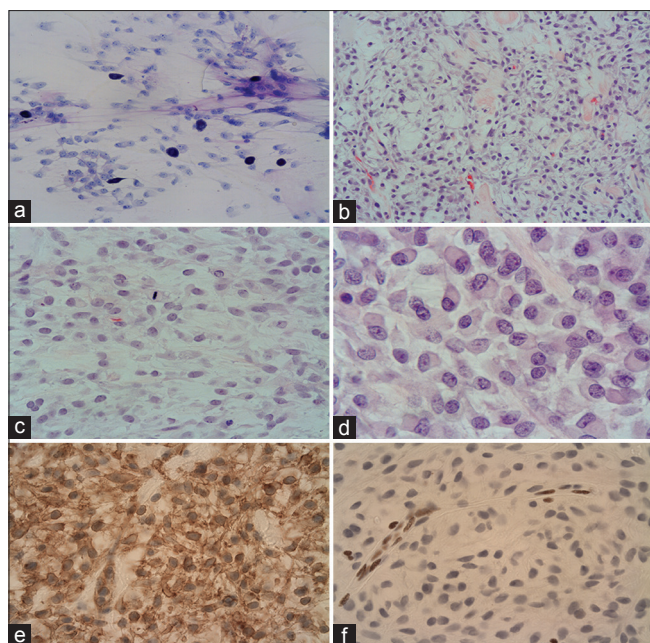


Figure 2: Toluidine blue stained smear preparation (a) shows spindle shaped, monomorphic neoplastic cells with prominent nucleoli in a loose matrix and mast cells. Epithelioid and spindle-shaped cells arranged in mucoid/myxoid background with hyalinised elements (b, c). The cytoplasm is frequently vacuolated and a mitotic figure is noted (c). Eosinophilic cytoplasmic inclusions in keeping with rhabdoid cells (d). Strong, diffuse immunoreactivity with CD34 (e). Loss of expression in the tumor cells by INI1, while the nuclear staining is preserved in the endothelial cells (f)

Focal mitotic activity was evident in addition to a few necrotic foci.

Immunohistochemistry showed strong, diffuse positivity with vimentin, synaptophysin, CD34 [Figure 2e], calretinin and in almost all cells with smooth muscle actin (SMA). EMA was focally positive and with a paranuclear dot-like immunoreactivity in a few cells. There was focal positivity with pan-neurofilament and neurofilament 200 KD. Pan-cytokeratin, MNF116, desmin, CD31, LICAM, AFP, STAT6, S100, IDH1, CD99, histone 3 (H3K27M) and GFAP were negative. ATRX showed preserved nuclear staining. The INI1 (BAF47) was negative in the tumor cells [Figure 2f]. The proliferation index was estimated between 12–15% by Ki67.

There was no evidence of mutations of BRAF V600E, IDH1, and IDH2 by pyrosequencing methods from genomic DNA extracted from formalin fixed paraffin embedded tissue. There was also no evidence of a KIAA1549-BRAF gene fusion by RT-PCR analysis. The MGMT promoter was unmethylated.

DISCUSSION

The presence of rhabdoid cells and the lost INI1 (BAF47) expression in an intracranial location would usually

confirm the diagnosis of atypical teratoid/rhabdoid tumor (AT/RT).^[15] Bi-allelic inactivation of SMARCB1 is not limited to AT/RT, however, and also includes extracranial soft tissue tumors (extrarenal malignant rhabdoid tumor (MRT), epithelioid sarcoma, some extraskeletal myxoid chondrosarcomas, some epithelioid malignant peripheral intracranial nerve sheath tumors, and some myoepithelial tumors).^[9] In our case, there was no evidence of a primary soft tissue tumor elsewhere and the immunophenotype also did not support any of those tumors above. The spectrum of known intracranial SMARCB1-deficient tumors mostly includes pediatric tumors, in addition to the well-known AT/RT, such as the benign cribriform neuroepithelial tumor (CRINET) and the rare poorly differentiated chordomas.^[4,11] There was no cribriform pattern or bone involvement in our case, however, the overall histological features were slightly atypical for AT/RT. For example pediatric AT/RTs are usually positive with cytokeratin unlike here. In addition, the composite rhabdoid tumors most often occur in adults arising from a pre-existing low grade glioma, such as pleomorphic xanthoastrocytoma (PXA).^[5,14,17] In addition to lack of morphological resemblance to PXA, we excluded glioma by negative GFAP and absence of common molecular glioma markers, such as IDH1/2 and BRAF V600E mutation. Dadone *et al.* emphasized the EMA and CD34 immunoreactivity of their cases, in addition to the smooth muscle actin and focal neurofilament positivity.^[6] It appears that the immunophenotype in our case is almost identical to those of Dadone *et al.* However, they claimed meningeal origin of their tumors based on the attachment to the dura and the strong EMA positivity. Our case was not attached to the dura although reached the cerebral surface radiologically. In addition, the strong synaptophysin positivity also argues against meningeal origin.

We have reviewed our departmental database going back to 1995 for AT/RT and performed immunohistochemistry in selected cases if necessary to confirm the diagnosis. Altogether we found 10 cases of INI1-deficient tumors [unpublished results]; the majority occurred in early childhood (age range 4 months to 2 years) and only two occurred in adults (49 year old female patient with pituitary AT/RT and the current case).^[3] Meningeal infiltration was confirmed in two pediatric cases. The majority had SMA (70%) and calretinin positivity (90%). At least focal CD34 immunoreactivity was detected in 6 cases but only one pediatric and the current adult case showed extensive positivity. CD34, although rarely performed routinely, is reported to be positive in 27% of the AT/RT cases in the literature.^[7]

The prognosis of the adult intracranial AT/RT is still to be determined. A recent literature review of 50 adult AT/RT cases found the median time to progression was 5 months and the overall survival was 23 months.^[7] The same study

concluded that presence of leptomeningeal metastases at the time of the operation significantly reduced the overall survival. Dardis *et al.* hypothesized that residual undifferentiated ectoderm in the circumventricular organs, particularly the pituitary and pineal glands, is the most common origin of adult ATRT/MRT, predisposing to early leptomeningeal dissemination.^[7] They also found that glial differentiation (GFAP staining) was strongly associated with leptomeningeal metastases predicting markedly worse outcomes. Nevertheless, it is important to note that case 1 described by Dadone *et al.* has survived 7 years after complete surgical resection and radiotherapy and there are at least four other cases in the literature with more than three years survival.^[1,6,7,13]

Our current case also occurred in a peripheral location of the frontal lobe with no connection to the ventricular system and the surgical resection appeared to be complete. Moreover the mitotic activity was low and the proliferation activity was moderate, corresponding to the relatively long history of 15 months prior surgery in our case. Post-operatively the patient recovered with normal power in her hand. Recurrent focal seizure activity was controlled increasing the dose of levetiracetam. Whole neuraxis MRI was performed after the histology result for disease staging and no spinal secondary deposit was identified [Figure 1e-f]. She was discharged with planned further adjuvant chemo/radiotherapy as per the AT/RT protocol, a pediatric protocol which recognizes adult presentation.

CONCLUSIONS

In conclusion, as an addition to the two cases of adult SMARCB1-deficient tumors recently described, we further present an adult case with a similar immunohistochemical profile but with an apparent intra-axial origin, questioning the necessary meningeal origin of this type of tumor. The prognosis of this adult INI1/SMARCB1-deficient tumor is to be determined, but may be better than the pediatric AT/RT.

Acknowledgement

Informed consent was obtained from the patient for publication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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