Letter

A novel *KDM2A::YAP1* fusion in a pediatric supratentorial CNS neoplasm resembling a tumor with *BCOR* internal tandem duplication

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Introduction

The central nervous system (CNS) tumor with *BCOR* internal tandem duplication (ITD), initially named high-grade neuroepithelial tumor (HGNET), was introduced as a novel embryonal neoplasm in the last World Health Organization (WHO) Classification of CNS tumors and in the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) classifier as a distinct methylation class (1,2). Since its initial description, other alterations of *BCOR* and its ligand *BCORL1* have been reported in CNS tumors having similar histopathological features. Among them, the fusion *EP300::BCOR* was evidenced in several cases with a distinct methylation class (3,4). Moreover, CNS tumors harboring fusions implicating other genes of the complex polycomb repressive complex 1.1 (PRC1.1) (*KDM2B* and *NUTM2A/B* genes) have been described (5). Herein, we report a brain neoplasm presenting the histopathological features of a CNS tumor with *BCOR* ITD, but harboring a *KDM2A::YAP1* fusion.

Case presentation

A 10-year-old boy presented with intracranial hypertension, found to be caused by a supratentorial (ST) intraventricular neoplasm. Magnetic resonance imaging (MRI) revealed a large mass within the left lateral ventricle having solid and cystic content (MRI performed after cyst aspiration) (**Figure 1B–F**). Computerized tomography (CT) showed the solid component to have intermediate density and calcification (**Figure 1A**), intense contrast enhancement (**Figure 1D**), and no diffusion restriction (**Figure 1E**). The tumor was subtotally resected. Morphologically, this tumor was mainly well-circumscribed from the brain parenchyma (with few infiltrating isolated cells around the periphery of the tumor). Pseudorosettes, microcysts and calcifications were observed (**Figure 2A–B**). There was no necrosis or microvascular proliferation, but the tumor presented a high mitotic count (6 mitoses per 5 high-power fields representing 1.6 mm^2) and proliferation index (10 %). Immunohistochemistry (IHC) confirmed the preserved expression of H3K27me3, INI1 and ATRX. There was no immunopositivity for GFAP, OLIG2 or MN1, and the expression of EMA was cytoplasmic without dot-like or microlumen staining. NeuN and neurofilament were expressed by a subset of tumor cells, and nuclear translocation of β-catenin was present. There was a weak, but diffuse, immunoreactivity for BCOR (**Figure 2C**) and a focal positivity for SATB2 (**Figure 2D**). RNA sequencing evidenced a *KDM2A::YAP1* gene fusion (**Figure 2E**). Next-generation sequencing failed to reveal any other alteration. The tumor was not classifiable using the Heidelberg Brain Tumor and sarcoma (v12.8) or Bethesda Classifiers, nor by t-Distributed Stochastic Neighbor Embedding (t-SNE) or Uniform Manifold Approximation and Projection (UMAP) analyses (**supplementary Figure 1**), which included HGNET-*BCOR* and sarcomas with *BCOR* alterations and CNS and soft tissue tumors with *YWHAE:NUTM2* or *KDM2B* fusions from our in-house database and previously reported (5). Forty-two months later, the patient presented a local recurrence of the tumor and a second surgery was performed. The recurrence histopathology was identical to the initial resection. The patient is alive without residue 60 months after the initial diagnosis and without any adjuvant treatment.

Discussion and conclusions

In the Heidelberg classifier (v12.8), two distinct methylation classes of CNS tumors characterized by different *BCOR* alterations exist: CNS tumors with *BCOR* ITD and those with *EP300::BCOR* fusion, with only the first being part of the current WHO classification (2). Regarding data from the literature (n = 82), CNS tumors with *BCOR* ITD affect mainly children (95 % of reported cases are pediatric with a median age of 3.5 years-old) and are distributed supratentorially and infratentorially (58 % and 42 % of reported cases, respectively) with a poor outcome (37 % patients were dead with a median overall survival of 20 months) (6–20). Contrarily, CNS tumors with an *EP300:BCOR* fusion (n = 24) concern young adults (median age of 28 years-old), are mostly supratentorial (83 % of reported cases) and seem to be associated with a better prognosis (no death reported to date in the literature and a median overall survival of 16 months) (3,4,16). Whereas CNS tumors with a *EP300::BCOR* fusion can present a broad histological spectrum (4), these two molecular entities may share similar histopathological features: a predominantly solid growth pattern, uniform oval or spindle-shaped cells with round to oval nuclei, a dense capillary network, and pseudorosette formations (3). Because of the nature of the antibody, only tumors with *BCOR* ITD showed a constant overexpression of the BCOR protein using IHC (4,21). In the literature, other alterations implicating the *BCOR* gene (*CREBBP::BCOR* fusions) or its ligand BCORL1 (*EP300::BCORL1, CREBBP::BCORL1* fusions) have been reported (16,22,23), for which SATB2 IHC may constitute a helpful diagnostic tool, being positive in CNS tumors with *BCOR* alterations (regardless of their molecular abnormality), and in sarcoma harboring *KDM2B* or *YWHAE* fusions (1,2). The current case showed a focal positivity for this antibody.

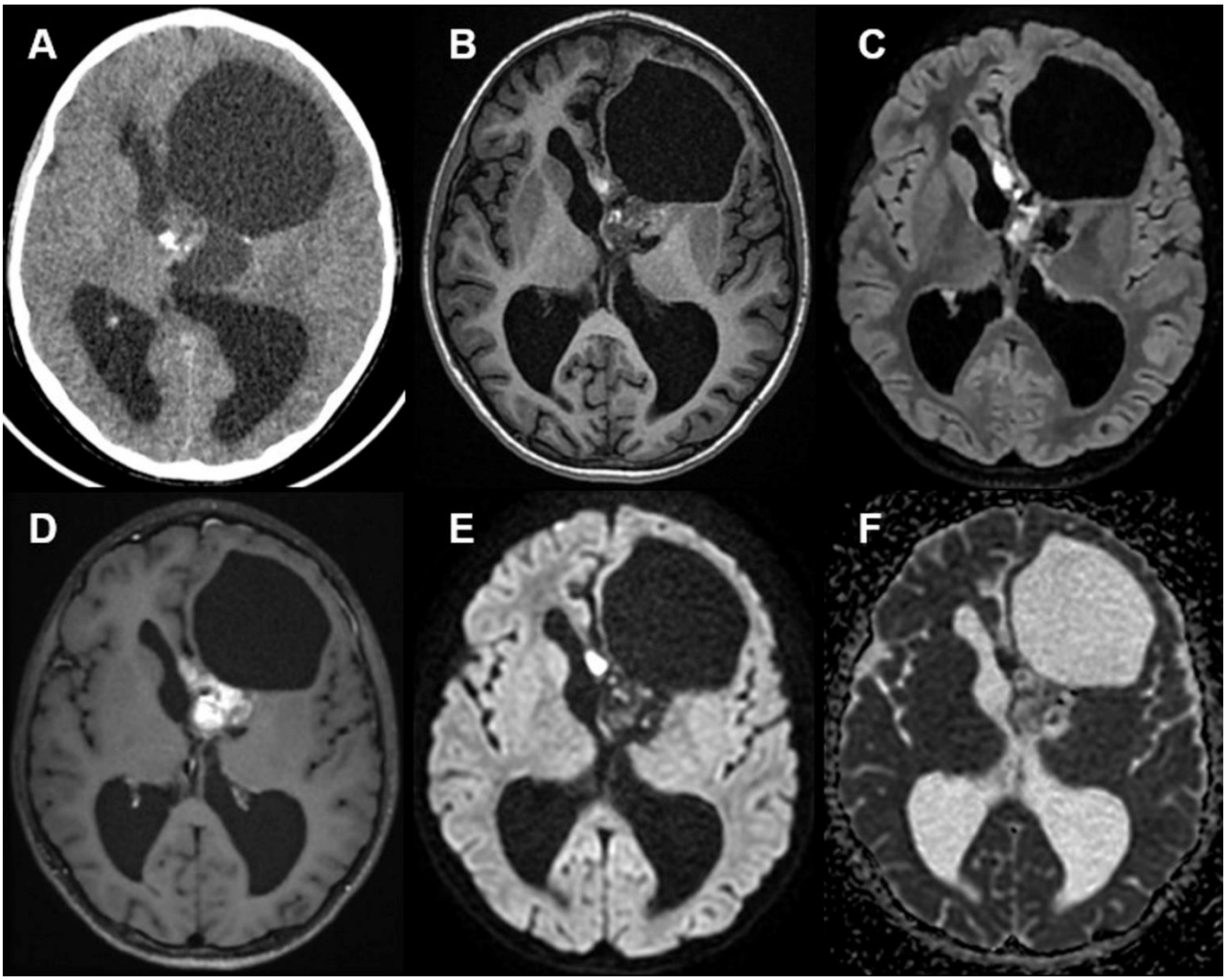

Figure 1. Radiological features: Axial unenhanced CT(**A**), T1-weighted (**B**), FLAIR (**C**), post-contrast T1-weighted (**D**), diffusion (**E**), and apparent diffusion coefficient (ADC) map (**F**) images of the patient, showing a large mass within the left lateral ventricle having solid and cystic content (MRI performed after cyst aspiration). CT showed the solid component to have intermediate density and calcification, intense contrast enhancement, and no diffusion restriction.

Interestingly, this case along with other rare CNS tumors and soft tissue/visceral sarcomas which have been found to harbor classically *BCOR* alterations, have been shown to have *KDM2A* or *KDM2B* fusions (5,24,25). Associated with BCOR in the PRC1.1 complex, KDM2A and B (Lysine Demethylase 2A and B) proteins mediate the transcriptional repression of tumor suppressors through the post-translational modifications of histones. The predicted fusion protein of the current case maintained major functional domains, such as the jumonji C and CXXC DNA-binding domains of the *KDM2A* gene and the WW domain of the *YAP1* gene which is a transcriptional co-activator as previously described (2,5). *YAP1* fusions are well known in the tumorigenesis of ependymomas (EPN) and it has been evidenced that they are sufficient to form tumors in the developing mouse brain (3). Moreover, the over-expression of the YAP1 protein in cortical progenitor cells induces an activation of the Hippo pathway and is implicated in cell proliferation (3).

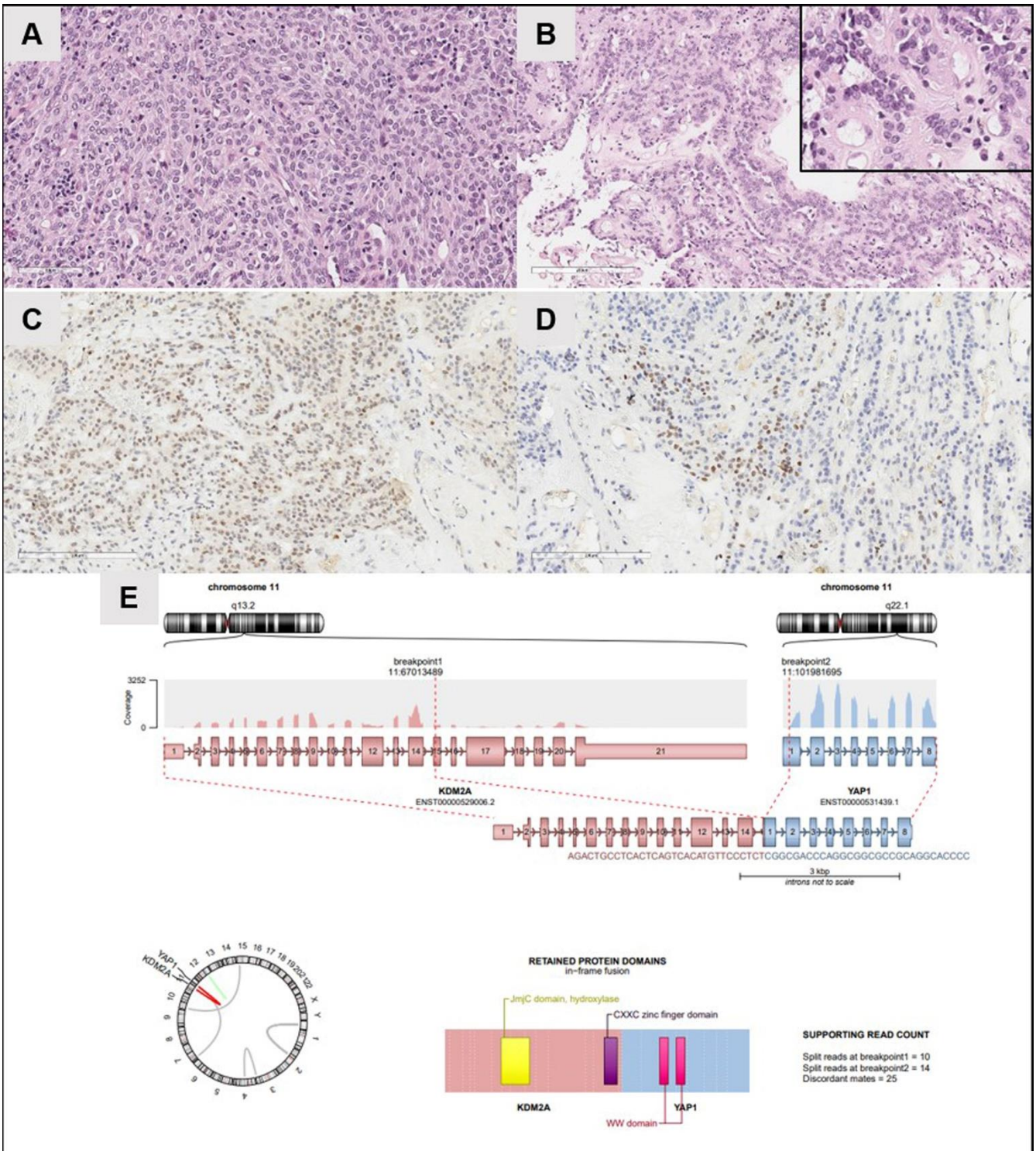

Figure 2. Histological and molecular features: The tumor was solid and composed of uniform oval or spindle-shaped cells with round to oval nuclei, a dense capillary network (**A**, Hematoxylin phloxin saffron (HPS), magnification x400), pseudorosettes and microcystic formations (**B**, HPS, magnification x400). BCOR protein immunoreactivity was weak in the tumor cells (**C**, magnification x400). Expression of SATB2 in a subset of tumor cells (**D**, magnification x400). **E** RNA-sequencing analysis evidenced a *KDM2A::YAP1* fusion.

In contrast to previously reported CNS cases harboring an alternative gene fusion of the PRC1.1 complex, the current tumor presented histopathological similarities to CNS tumors with *BCOR* alterations but not sarcomas (5). However, the DNA-methylation analysis did not permit its classification. This is potentially due to the fact that only CNS tumors with *BCOR* alterations are present in the current classifier and that the boundaries of the current methylation classes are not clearly defined, with a subset of cases being misclassified (4,22). Other samples having these rare alterations are necessary to determine if they cluster together and form a distinct methylation class from those described.

In closing, we report herein a CNS tumor having histopathological similarities to CNS tumors with *BCOR* alterations, but having a fusion implicating the gene *KDM2A*, encoding a protein of the PRC1.1 complex. In cases of a suspected CNS tumor with *BCOR* alteration without a strong and diffuse immunopositivity for the BCOR protein, RNA-sequencing analysis may help to diagnose alternative fusions.

Ethics approval

This study was approved by GHU Paris - Psychiatry and Neuroscience, Sainte-Anne Hospital's local ethics committee.

Consent for publication

The patients signed informed consent forms before treatment began.

Conflict of interest

The authors declare that they have no conflicts of interest directly related to the topic of this article.

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