CNS Tumor with *BCOR* Internal Tandem Duplication: The First Case in Southeast Asia

Thitiporn Fangsaad[1] ; Surakarn Jansutjawan[2] ; Patsook Kittikakul[3] ; Siriluk Assawabumrungkul[1] ; Nattaporntira Phalakornkul [2]; Artit Jinawath[4] ; Chinnachote Teerapakpinyo[5] ; Thiamjit Chaichana[7]; Shanop Shuangshoti[5,6] ; Sakun Santisukwongchote[7]

Thitiporn Fangsaad

[1] Division of Neurology, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok, Thailand
[2] Division of Hematology and Oncology, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok, Thailand
[3] Division of Neurosurgery, Department of Surgery, Bhumibol Adulyadej Hospital, Bangkok, Thailand
[4] Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok
[5] Chulalongkorn GenePRO Center, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[6] Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[7] Department of Pathology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

** Address Correspondence to author:*
Sakun Santisukwongchote, MD
Department of Pathology,
13th floor of Or Por Ror Building,
King Chulalongkorn Memorial Hospital, Rama 4 Road,
Bangkok 10330, Thailand
email: boomskuun@gmail.com

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Abstract

The central nervous system (CNS) tumor with *BCOR* internal tandem duplication (ITD) or high-grade neuroepithelial tumor with *BCOR* alterations (HGNET-*BCOR*) has been proposed as a new entity of CNS embryonal tumor. We report herein the first case of CNS tumor with *BCOR* ITD in Southeast Asia. The patient was a 2-year-old girl who presented with head tilt and ataxia. CNS showed a posterior fossa mass, 5.7x5.2x4.2 cm, with faint enhancement and internal hemorrhage. The lesion was removed, and the pathological examination revealed a hypercellular tumor comprising neoplastic cells with oval hyperchromatic nuclei. Perivascular pattern was occasionally observed. Pseudopalisading necrosis was seen but microvascular proliferation was absent. Although the clinical features of HGNET-*BCOR* are not distinctive and may overlap with other high-grade primary CNS tumors, awareness of the pathological features and the positive *BCOR* immunostain should lead to a final diagnosis with the identification of *BCOR* ITD using a molecular method.

Keywords: embryonal CNS tumor, PNER, HGNET-*BCOR*, *BCOR*, brain tumor, CNS tumor with *BCOR* ITD

The term "primitive neuroectodermal tumor (PNET)" was coined by Hart and Earl[1] in 1973 to describe a malignant central nervous system (CNS) tumor that is commonly encountered in the early life. In the original description, most of the tumors share several common features, including cerebral location, grossly cystic and hemorrhagic with well-defined border, undifferentiated tumor cells with focal glial and neuronal differentiations, and mesenchymal component. Although the concept of PNET with divergent differentiations was remarkable at the time, it is now clear that CNS-PNET is not a single disease, and with advances in molecular biology, several distinct entities have been extracted from the so-called PNET.[2]

In 2017, Sturm et al.[2] proposed four new brain tumor entities occurring in children with CNS-PNET features: CNS neuroblastoma, *FOXR2* activated, *CIC*-rearranged sarcoma, astroblastoma, *MN1*-altered, and CNS tumor with *BCOR* ITD.

CNS tumor with *BCOR* ITD is a distinct molecularly-defined CNS tumor with an in-frame internal tandem duplication in exon 15 of *BCOR* gene, with only 27 cases having been previously reported.[2-7] Awareness of the new tumor entities is crucial for pathologists to reach the correct diagnosis. Here, we report another example of CNS HGNET-*BCOR*, which appears to be the first case recorded in Southeast Asia.

Case Report

Two days prior to seeking medical attention, a 2-year-old previously healthy girl experienced vomiting, head tilt, and ataxia. Her vital signs were normal. The head tilted to the right side, with chin deviated to the left. Neurological examination demonstrated hyperreflexia and positive Babinski sign bilaterally, with presence of clonus and truncal ataxia. The cranial nerve functions and the power motor were intact. A computed tomography scan at a private hospital showed a 5-cm non-enhancing hypodensity tumor at the left superior aspect of cerebellum. Further magnetic resonance imaging (MRI) at Bhumibol Adulyadej Hospital showed a left superior cerebellar mass (5.7x5.2x4.2) (Figure 1A), with faint enhancement, internal hemorrhage, pressure effect, with tonsillar herniation and early obstructive hydrocephalus (Figure 1B and C). A highly cellular neoplasm was suggested by the reduced diffusion observed by diffusion weighted imaging (Figure 1D).

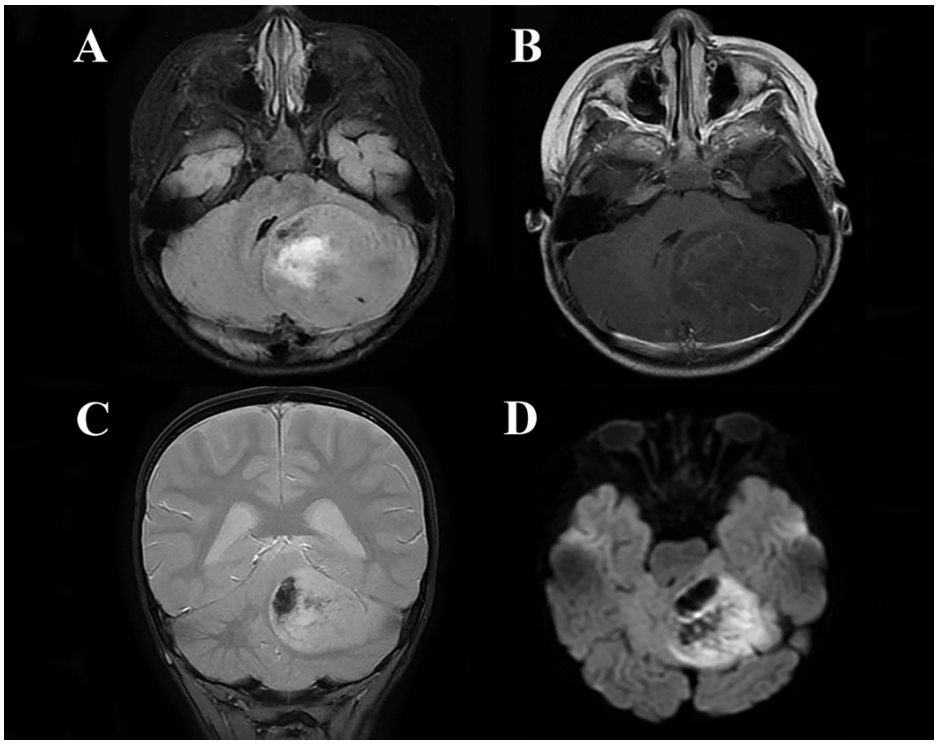

Figure 1: MRI shows a mass at the left superior cerebellum, measuring 5.7x5.2x4.2 cm (A). Faint enhancing (B) with internal hemorrhage (C) is noted, causing pressure effect and tonsillar herniation. Diffusion weighted imaging (D) showed reduced diffusion, suggestive of a hypercellularity neoplasm.

The patient underwent partial tumor removal with ventriculoperitoneal shunting. Pathological examination showed a hypercellular tumor. Numerous tumor cells with uniformly oval-shaped, hyperchromatic nuclei but indistinct nucleoli were seen. Occasional perivascular patterns/ pseudorosettes were noted. Cytoplasmic processes were suggested by the routine stain but not distinctive. Microcysts were occasionally seen. Mitotic figures were up to 10/10 high-power field, with apoptotic nuclei identified. Multiple foci of palisading necrosis were present while microvascular (so-called "endothelial") proliferation was absent. With the immunohistochemical study, diffuse and strong nuclear expression with BCOR (clone C10, sc-514576; Santa Cruz, Dallas, TX) was observed. Rare tumor cells were reactive with Olig2. The neoplastic cells were non-reactive with GFAP, synaptophysin, neurofilament protein, and NeuN. Nuclear expression of INI1 and ATRX was preserved. H3 K27M was negative. Ki-67 index was up to 30% in hot spot areas.

Molecular study demonstrated internal tandem duplication within exon 15 of the *BCOR* gene. Next-generation sequencing (Oncomine Comprehensive Assay, Thermo Fisher Scientific) did not identify additional mutations.

The patient was stable post-operatively. Initially, the parents denied further treatment because of the poor prognosis and treatment discomfort. Five months after the surgery, the patient was moved to Ramathibodi Hospital where she underwent a second operation, followed by an infant brain protocol chemotherapy. The third operation was carried out 5 months afterwards, and it was followed by a concurrent chemoradiation using the regimen for recurrent medulloblastoma. The latest imaging study, 1.5 years after the onset, revealed a non-enhancing residual tumor with isointense T1, slightly hyperintense T2, and restricted diffusion, along the superoposterior aspect of the surgical cavity. The patient survived at 1 year and 10 months with a residual tumor.

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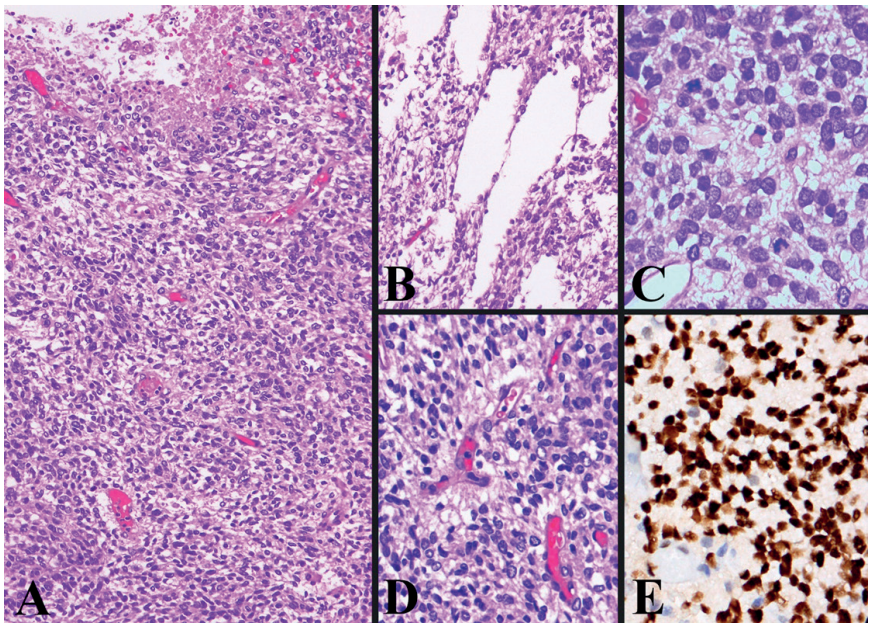

Figure 2: Hematoxylin and eosin stain reveals a highly cellular tumor, containing foci of necrosis (A), note a necrotic area at the most upper part). Uniform neoplastic cells with oval-shaped hyperchromatic nuclei are noted. Microcysts are present (B), and fibrillary background is suggested. Perivascular pattern is occasionally seen, without microvascular proliferation (C). There are numerous mitotic figures (D). The tumor cell nuclei strongly expresses BCOR protein (clone C10, sc-514576; Santa Cruz, Dallas, TX) (E).

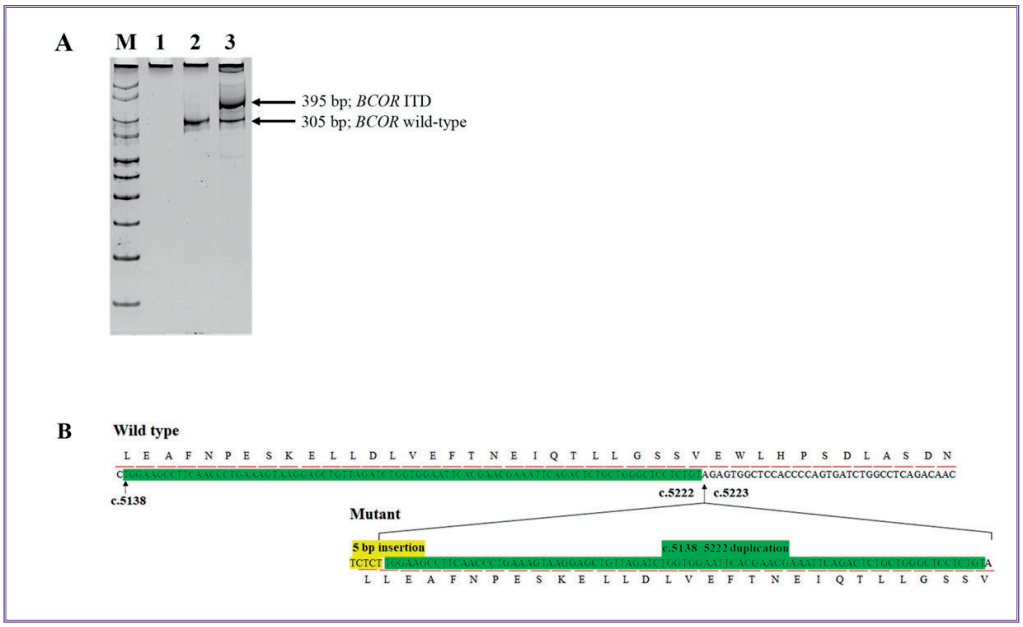

Figure 3: Internal tandem duplication (ITD) detection in *BCOR* by reverse transcription PCR (RT-PCR) and direct sequencing. (**A**) *BCOR* exon 15 was amplified in normal (wild type) sample (lane 2) and the patient's sample (lane 3) showing both expected 305 bp wild type amplicon and 395 bp ITD amplicon. Lane M; 25 bp marker, lane 1; no template control. (**B**) The ITD sequence was analyzed using RT-PCR and direct sequencing. The result showed c.5222_5223insTCTCTdup85 consisting of 5-bp insertion and 85-bp upstream duplication at c.5222_5223 residing in *BCOR* exon 15 (NM_001123385.2). The arrow indicates start site of 5-bp insertion and 85-bp upstream ITD. The nucleotide sequence of 5-bp insertion and 85-bp upstream ITD are shown in yellow and green highlights, respectively.

Discussion

CNS tumor with *BCOR* ITD is a rare and recently proposed embryonal CNS tumor. Before its description, the tumor was diagnosed as a high-grade tumor, such as glioblastoma, CNS-PNET, atypical teratoid rhabdoid tumor, medulloblastoma, and anaplastic ependymoma. CNS tumor with *BCOR* ITD carries a dismal prognosis, and the optimal therapeutic treatment protocol is not yet established. Thus far, 27 cases of CNS tumor with *BCOR* ITD have been reported.[3-13] Including our case (28 cases in total), the patients' age ranges from 7 months to 22 years (mean 5.3 years). The most common site is the posterior fossa (19/28, 67.9%), followed by the frontal lobe (6/28, 21.4%), and other areas including the parieto-occipital lobe (1), the temporal lobe (1), and the basal ganglia (1). Radiologically, CNS tumor with *BCOR* ITD shares features with other high-grade neoplasms including enhancement and reduced diffusion[10].

Histopathologically, CNS tumor with *BCOR* ITD is highly cellular, consisting of tumor cells with round-to oval-shaped hyperchromatic nuclei, indistinct nucleoli, and scant eosinophilic cytoplasm. As in our case, some cases contain tumor cells with oval-shaped nuclei with the suggestion of cytoplasmic processes. Tumor cells with vacuolated cytoplasm may also be encountered. Perivascular pseudorosettes are commonly present. Mitotic figures range from 4 to 24 mitoses/10 HPFs. While necrosis is often seen as noted in our case, microvascular proliferation has not been observed. With the immunohistochemical study, vimentin is reactive in most cases. GFAP is often negative or only focally positive in some cases. In contrast to ependymal tumors, the perivascular zone of the pseudorosettes in CNS tumor with *BCOR* ITD lacks GFAP expression. The S-100 protein staining pattern resembles that of the GFAP. Although most cases were reported to express Olig2, the percentage of positive cells and intensity varied. Nuclear expression of β-catenin was observed in up to 79% of the cases.[2] MIB-1 proliferative index ranges from 12% to 52.7%. All cases, including ours, show strong and diffuse nuclear expression of *BCOR*. The immunoreactivity of *BCOR* is not only found in tumors with *BCOR* alterations in various forms, including fusions and ITD, but also in normal tissue with high *BCOR* protein expression such as testis.[14-16] Furthermore, the *BCOR* immunostain may also occur in other tumors, such as medulloblastoma and solitary fibrous tumor.[3,4,5,7] Therefore, it is important to be keep in mind that the positive *BCOR* immunostain is not a mutation-specific antibody, or specific for CNS tumor, with *BCOR* ITD[3], and the positive immunostain needs further verification with a molecular method to identify *BCOR* ITD.[3,4,5,7]

BCL-6 transcriptional corepressor (*BCOR*) gene is located at Xp11.4. *BCOR* protein contains two main functional binding domains, including the BCL-6 binding domain and Polycomb-group RIG finger homolog (PCGF) ubiquitin-like fold discriminator.[17,18] The protein functions as a transcriptional corepressor with BCL-6, and as histone modification. *BCOR* alterations have been identified not only in CNS tumor with *BCOR* ITD, but also in a broad spectrum of neoplasms, including clear cell sarcoma of the kidney, primitive myxoid mesenchymal tumor of infancy, high-grade endometrial stromal sarcoma, ossifying fibromyxoid tumour, acute myeloid leukemia, and undifferentiated round cell sarcoma.[2,3,16] Although the ITD in PCGF ubiquitin-like fold discriminator domain is also found in the clear cell sarcoma and the primitive myxoid mesenchymal tumor, it is unclear now as to whether all *BCOR* ITD-positive tumors occurring at different locations should be grouped into one entity.[3-5,17-19] *BCOR*-fusion features in all the remainder.[17,20,21] The negative result of our comprehensive gene panel testing supports that the *BCOR* alteration appears to be the important oncogenic driver in this tumor.

The standard treatment protocol for CNS tumor with *BCOR* ITD is not yet established, given its rarity. Gross total resection, followed by adjuvant treatments including chemotherapy and/or radiotherapy, is the preferred option.[10,11] Multiple regimens of chemotherapy and craniospinal irradiation have been proposed.[11,12] The outcome of patients with CNS tumor with *BCOR* ITD is generally poor, with tendency to relapse and metastasis.[10,11] Further study is needed to provide more insight to this rare CNS tumor.

Conclusion

The first case of CNS tumor with *BCOR* ITD in the Southeast Asia has been documented. The diagnosis of brain tumors is an evolving field, faced with the challenge of keeping up with advances in molecular pathology. The new WHO classification of CNS tumors contains several new diagnoses extracted from the older entities. Awareness of the new tumors is the key to arrive the correct diagnosis.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Hart MN, Earle KM. Primitive neuroectodermal tumors of the brain in children. *Cancer* 1973;32:890-7.
2. Sturm D, Orr BA, Toprak UH, et al. New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs. *Cell*. 2016;164:1060-72.
3. Haberler C, Reiniger L, Rajnai H, et al. Case of the month 1-2019: CNS high-grade neuroepithelial tumor with BCOR alteration. *Clin Neuropathol.* 2019;38:4-7.

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4. Ferris SP, Velazquez Vega J, Aboian M, et al. High-grade neuroepithelial tumor with BCOR exon 15 internal tandem duplication-a comprehensive clinical, radiographic, pathologic, and genomic analysis. *Brain Pathol.* 2020;30:46-62.
5. Appay R, Macagno N, Padovani L, et al. HGNET-BCOR Tumors of the Cerebellum: Clinicopathologic and Molecular Characterization of 3 Cases. *Am J Surg Pathol.* 2017;41:1254-60.
6. Paret C, Theruvath J, Russo A, et al. Activation of the basal cell carcinoma pathway in a patient with CNS HGNET-BCOR diagnosis: consequences for personalized targeted therapy. *Oncotarget.* 2016;7:83378-91.
7. Yoshida Y, Nobusawa S, Nakata S, et al. CNS high-grade neuroepithelial tumor with BCOR internal tandem duplication: a comparison with its counterparts in the kidney and soft tissue. *Brain Pathol.* 2018;28:710-20.
8. Paret C, Russo A, Otto H, et al. Personalized therapy: CNS HGNET-BCOR responsiveness to arsenic trioxide combined with radiotherapy. *Oncotarget*. 2017;8:114210-25.
9. Kline CN, Joseph NM, Grenert JP, et al. Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro Oncol.* 2017;19:699-709.
10. Al-Battashi A, Al Hajri Z, Perry A, et al. A Cerebellar High-Grade Neuroepithelial Tumour with BCOR Alteration in a five-year-old Child: A case report. *Sultan Qaboos Univ Med J.* 2019;19:e153-e6.
11. De Lima L, Surme MB, Gessi M, et al. Central nervous system high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)-case-based reviews. *Childs Nerv Syst.* 2020;36:1589-99.
12. Rao S, Mitra S, Sugur H, et al. Central nervous system high grade neuroepithelial tumor with BCOR immunopositivity: Is there a molecular heterogeneity? *Brain Tumor Pathol.* 2021;38:41-9.
13. Kirkman MA, Pickles JC, Fairchild AR, et al. Early Wound Site Seeding in a Patient with Central Nervous System High-Grade Neuroepithelial Tumor with BCOR Alteration. *World Neurosurg.* 2018;116:279-84.
14. Mariño-Enriquez A, Lauria A, Przybyl J, Ng TL, Kowalewska M, Debiec-Rychter M, et al. BCOR Internal Tandem Duplication in High-grade Uterine Sarcomas. *Am J Surg Pathol.* 2018;42(3):335-41.
15. Kao YC, Sung YS, Zhang L, Jungbluth AA, Huang SC, Argani P, et al. BCOR Overexpression Is a Highly Sensitive Marker in Round Cell Sarcomas With BCOR Genetic Abnormalities. *Am J Surg Pathol.* 2016;40(12):1670-8.
16. Khan MZ, Akhtar N, Hassan U, Mushtaq S. Diagnostic Utility of BCOR Antibody in Clear Cell Sarcomas of Kidney. Int *J Surg Pathol.* 2020;28(5):477-81.
17. Aldera AP, Govender D. Gene of the month: BCOR. *J Clin Pathol.* 2020;73:314-7.
18. Astolfi A, Fiore M, Melchionda F, et al. BCOR involvement in cancer. *Epigenomics.* 2019;11:835-55.
19. Kao YC, Sung YS, Zhang L, et al. Recurrent BCOR Internal Tandem Duplication and YWHAE-NUTM2B Fusions in Soft Tissue Undifferentiated Round Cell Sarcoma of Infancy: Overlapping Genetic Features With Clear Cell Sarcoma of Kidney. *Am J Surg Pathol*. 2016;40:1009-20.
20. Lewis N, Soslow RA, Delair DF, et al. ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity. *Mod Pathol.* 2018;31:674-84.
21. Specht K, Zhang L, Sung YS, et al. Novel BCOR-MAML3 and ZC3H7B-BCOR Gene Fusions in Undifferentiated Small Blue Round Cell Sarcomas. *Am J Surg Pathol.* 2016;40:433-42.