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Academic article

BCOR-CCNB3 fusion-positive soft tissue sarcoma: A case report and literature review

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Abstract

BCOR-CCNB3 sarcoma is one of a group of undifferentiated sarcomas. The objective of this case report was to describe the clinical and pathological data of a patient with this tumor. Our patient was a 14-year-old male adolescent with right flank pain. Imaging revealed a psoas muscle mass lesion. Histology and gene expression were suggestive of BCOR-CCNB3 sarcoma. Chemotherapy, surgery, and radiotherapy were used according to the Ewing sarcoma protocol in Thailand. Unfortunately, our patient died from acute myeloblastic leukemia (M5) without remission despite chemotherapy.

Keywords: BCOR-CCNB3 sarcoma, undifferentiated sarcoma, acute myeloblastic leukemia

Introduction

BCOR-CCNB3 sarcoma results from a paracentric inversion on the X chromosome and fusion between *BCOR* (encoding the BCL6 co-repressor) and *CCNB3* (encoding the testis-specific cyclin B3), and it was first reported in 2012.[1] The clinicopathological and chromosomal abnormalities of this tumor are distinctive from those of known sarcomas such as Ewing sarcoma, synovial cell sarcoma, or rhabdomyosarcoma. To date, most reports of BCOR-CCNB3 sarcoma have been based on undefined diagnostic tissue.[2–9]

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Kao et al. reported four recently diagnosed cases of BCOR-CCNB3 sarcoma, and some were still in the process of treatment.[9] Here, we report the clinical presentation, investigation, and treatment outcome of a newly diagnosed case of BCOR-CCNB3 sarcoma.

Case report

A 14-year-old male adolescent presented with right flank pain for 1 week. He had dull right intermittent abdominal pain that later moved to his right flank. He denied experiencing nausea, vomiting, abnormal urination, or weight loss. He only had a low-grade fever. Four months previously, he had similar pain, but it had resolved with rest and paracetamol. He also had a motorcycle accident between the episodes of pain, during which he felt normal. His family had no history of malignancy. Physical examination revealed only mild tenderness in his right flank. Complete blood count was unremarkable, and urinalysis showed microscopic hematuria (3–5 red blood cells/high-power field).

The kidneys, ureters, bladder (KUB) ultrasonography showed a 9.9 x 6.3 cm well-defined oval heterogeneous hypoechoic mass with internal cystic foci at the right suprarenal region, with no calcification or increased vascularity. The lesion was inseparable from the head of the right psoas muscle. Abdominal computed tomography (CT) revealed a 4.8 x 6.3 x 10.3 cm (anterior-posterior (AP) x transverse x cranio-caudal (CC)) lobulated well-defined heterogeneous hypodense mass (20–40 HU), with irregular rim enhancement at the head of the right psoas muscle. Thin peripheral rim calcification and tiny calcific foci were seen (Figure 1). The differential diagnoses were resolving hematoma or tuberculosis abscess. Follow-up CT 4 weeks later showed that the lesion had increased in size, with the development of a thicker and more irregular rind of peripheral enhancement. Focal bone erosion of the adjacent medial end of the lower thoracic rib was also observed. These findings raised the suspicion of a tumor rather than an infectious process.



Figure 1. Computed tomography showed a well-defined heterogeneous hypodense mass with irregular rim enhancement in transverse and coronal plane.

A needle biopsy was done under CT guidance. Specimens were sent for pathological and microbiological examination (aerobic bacteria, mycobacteria, and fungi). All infectious disease investigations were negative. Histopathology revealed small round to spindle cells arranged in clusters and solid sheets and embedded in fibromyxoid stroma. Immunohistochemical studies were positive for transducer-like enhancer of split 1 (TLE1)

and smooth muscle actin (SMA), and negative for CD3, CD99, desmin, anti-muscle actin antibody (HHF35), myogenin, paired box 5 (PAX 5), and Wilms' tumor 1 (WT1). Synovial sarcoma was suspected; therefore, RT-PCR was used to identify any *SYT-SSX* gene fusion. However, it was negative for both types 1 and 2. Thus, a second panel of immunohistochemical studies was performed for differential diagnosis of Ewing-like sarcoma. These results revealed focal positivity for BCOR and SATB2 and negativity for Bcl6. Additional RT-PCR confirmed a positive *BCOR-CCNB3* fusion transcript (Figure 2).

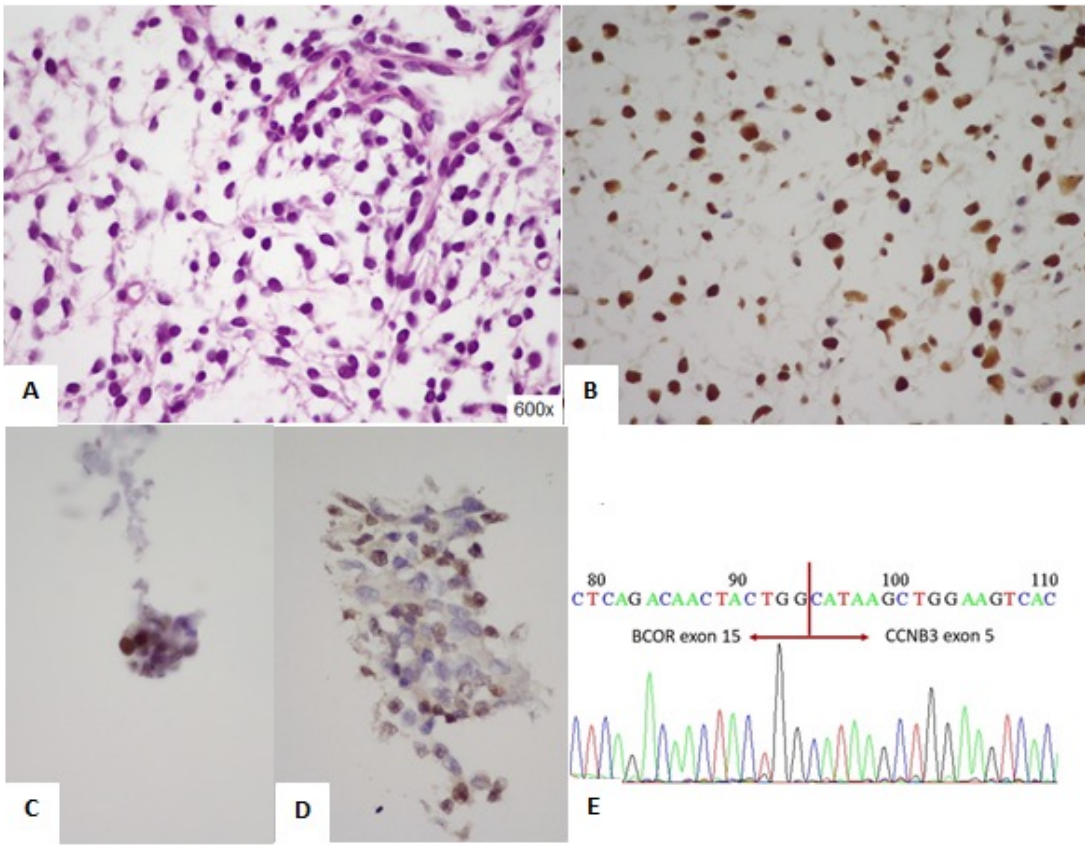


Figure 2. Histopathological examination of (A) small blue round cell neoplasm. (B)Positive staining for TLE1. (C) Positive staining for BCOR. (D) Positive staining for SATB2. (E) DNA sequencing demonstrating *BCOR-CCNB3* fusion.

While waiting for the pathological report, magnetic resonance imaging (MRI) and metastatic work-ups were done. Thoracolumbar spinal MRI showed a 7.0 x 8.9 x 10.8 cm (AP x transverse x CC) well-defined lobulated mass in the head of the psoas muscle. The mass was situated along the right paravertebral region, with a thicker rind of nodular intermediate T1W and hyperintense T2W signals, and heterogeneous enhancement on the postcontrast study. There were multiple internal linear hypointense signals at the periphery, and hyperintense T1W and hypointense T2W signals in the central area. The mass extended into the right lower intercostal paravertebral muscles, and right T12–L1 neural foramen, compromising T12 exiting nerve roots. It was also suspected to compromise the right T11–L2 intercostal nerves. Focal lytic destruction at the medial end of the right 12th rib was seen (Figure 3). Chest CT revealed a 0.5-cm nodule in the superior segment of the right lower lobe. Whole-body bone scintigraphy (Tc-99m MDP) demonstrated no evidence of bone metastasis. Bone marrow aspiration showed no abnormalities.

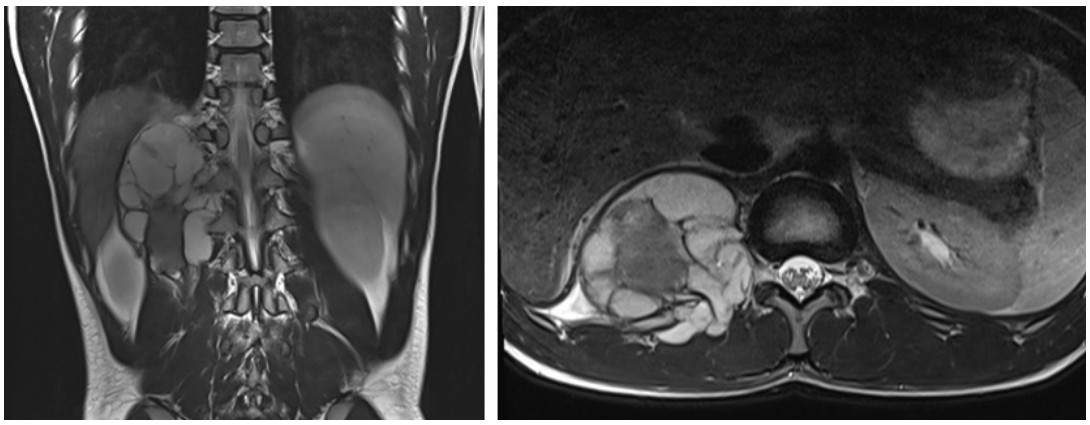


Figure 3. T2W signal and postcontrast study demonstrated involvement of the right 12th rib and neural foramen in transverse and coronal plane.

The definitive diagnosis was BCOR-CCNB3 sarcoma of the right psoas muscle. The Ewing sarcoma treatment protocol (Supplement 1: ThaiPOG-EWS-13SR)[10] was adopted for this patient. After neoadjuvant chemotherapy for six cycles, the mass shrunk to 3.6 x 6.6 x 10.8 cm but still involved nearby structures, as shown on previous MRI. We decided to perform *en bloc* resection with the 12th right rib and T12 and L1 nerve root via a flank incision. The postoperative course was uneventful. Pathological examination revealed a microscopic positive margin at the posterior side of the mass, and the rib bone was encroached by the tumor at the posterior margin. Tumor necrosis volume was about 50%. There was no demonstration of lymphovascular invasion (Figure 4)

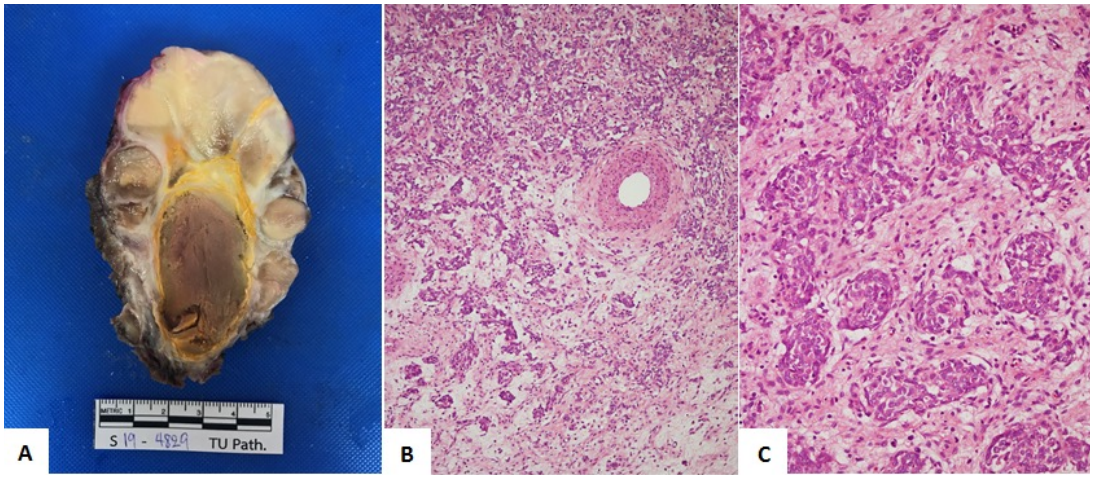


Figure 4. (A) Gross specimen from *en bloc* resection. (B) Solid sheets of neoplastic cells embedded in fibromyxoid stroma. (C) Small round to spindle cells arranged in clusters and solid sheets.

A total of 4500 cGy radiation was administered to the tumor base, divided into 25 fractions (1.8 Gy/fraction). Chemotherapy was continued until completion of 14 cycles. The primary site and lung metastasis were re-evaluated by MRI, which showed no residual tumor; chest CT revealed no change in the 0.5-cm nodule in the right upper lung; and bone scintigraphy found no bone metastasis. During treatment, our patient experienced neutropenia, phlebitis, and tinea versicolor as complications.

Four months after the end of treatment, he presented with a rash for 1 week, followed by fever for 1 day, without a history of bleeding. Physical examination revealed petechiae, generalized papules, and splenomegaly 8 cm below the left costal margin. Complete blood count showed pancytopenia: hemoglobin 8.1 g/dL, hematocrit 24.1 %, white blood cells 3,100 cells/mm^3 (neutrophil 15, lymphocyte 44, monocyte 33, eosinophil 1%), and platelets 7,000/mm^3. Bone marrow Wright's stain and clot marrow pathology revealed numerous medium to large blasts with round to oval nuclei 98%. Flow cytometry showed that the blast population expressed moderate intensity of CD45 and low to moderate complexity, representing around 77.60% of total events. This population was positive for CD11c, CD13 (partial), CD14 (partial), CD15, CD38, CD64, HLA-DR, and cMPO (partial). Therefore, he was diagnosed with acute myeloid leukemia (AML-M5). Chromosome from bone marrow presented 46, XY, ins (9; 11) (p13;q13q23). Skin biopsy revealed leukemic cutis. Whole exome sequencing reported three variants of unknown significance identified in the following 147 genes associated with myeloid leukemia as *BIRC3*, *FAM47A*, and *SETBP1*.

After he received chemotherapy using the AML protocol including idarubicin and cytarabine (7+3 regimen) for 1 month, bone marrow examination showed partial response. Therefore, he received re-induction chemotherapy, high-dose cytarabine (HiDAC). During treatment, he had infections that included febrile neutropenia, *Clostridium difficile* colitis, and invasive pulmonary aspergillosis. He did not reach remission of AML; therefore, he received palliative treatment and died from uncontrolled leukemia.

Discussion

To the best of our knowledge, this is the first patient diagnosed with BCOR-CCNB3 sarcoma of soft tissue in Thailand. As stated in other reports, BCOR-CCNB3 sarcoma occurs more often in bone than in soft tissue. Our patient was in the most common age group for this diagnosis; nearly all patients are in the second decade of life[2–9], with ages ranging from 2 to 44 years.[9] There is one report of a congenital case.[11] The supposed male predominance in all series[2–9] may have resulted from an inability to use another X chromosome as a template for meiosis repair; however, it is still unclear regarding mitosis in somatic cells.[4]

Our patient experienced only right flank pain, which is also typical of most patients. Other clinical signs are swelling, limping, pathological fractures, and mass effect symptoms.[2] The origin of this tumor is often in bone and soft tissue. BCOR-CCNB3 fusion is also found in kidney sarcoma.[12,13] Lung, bone, and liver metastases are other reported manifestations.[2,3,8] An MRI review of six cases of soft tissue sarcomas found well-defined borders to infiltrative, low to immediate signal intensity in T1, high signal intensity in T2, variably heterogeneous intensity in T2 with enhancement by gadolinium, focal necrotic or hemorrhagic area, or local invasion to adjacent bone.[2,6] Our MRI findings were similar to previous reports, but they cannot be specifically extrapolated for this disease. Our CT results were also not specific to the disease and mimicked an abscess or hematoma.

As this is a newly identified disease, there is no known treatment. More than half of the previously reported cases were treated by the Ewing sarcoma protocol [2,5]; thus, we attempted to do the same. As we have a national cancer protocol for pediatric cases in Thailand, the Thai POG-EWS-13SR protocol was applied. A partial response to our

chemotherapy was observed, but it provided less resection area. After completion of treatment, our team decided to closely observe a sub-centimeter lung nodule.

Secondary AML resulting from chemotherapy has been reported in many cases, but it usually occurs 2–3 years after epipodophyllotoxins (topoisomerase II inhibitors)[14] and 5–7 years after alkylating agents.[15] There are also reports of secondary AML after radiotherapy. In our patient, AML occurred only 4 months after the end of therapy, which is unusual. Several factors are reported to influence the risk of epipodophyllotoxin-related AML, such as frequency of administration, cumulative dose, concomitant chemotherapy or non-chemo therapeutic agents, and host factors.[16] In our case, the patient received etoposide 5 days per week in regimen B, with a cumulative dose of 3.5 g/m^2. The frequency and intermittent schedule of etoposide are both associated with greater risk of secondary AML.[17–19] The combination of epipodophyllotoxins and alkylating agents such as cyclophosphamide and ifosfamide, which were used for chemotherapy in our patient, has been associated with an increase of secondary AML.[20–22] Granulocyte colony-stimulating factor also may increase the incidence of secondary AML, but Bhatia et al. reported no association between granulocyte colony-stimulating factor administration and secondary AML in a group of children with Ewing sarcoma.[23] Smith et al. hypothesized that the incidence of secondary AML was lower in pediatric patients with solid tumors than in those with AML because of the different dosing schedule of epipodophyllotoxins.[24] Nowadays Meta-analysis of BCOR-rearranged sarcomas showed similar overall survival for patients who received Ewing sarcoma and non-Ewing sarcoma treatment protocols[25], therefore, we might use a non-Ewing protocol to avoid epipodophyllotoxins.

Mutations in the *BCOR* and *BCOR1* genes have been reported in AML in recent years. Grossmann et al. reported that, in adult AML with normal karyotype, *BCOR* gene mutations occurred in 4% of cases[26] and occasionally co-occurred with *FLT3-ITD* and *NPM1* mutations. In this case, we could not find the *BCOR* mutation or *FLT3-ITD* and *NPM1*. However, our patient had *BIRC3*, *FAM47A*, and *SETBP1*. *BIRC3* mutations are present in a wide range of epithelial tumors.[27] *SETBP1* is localized on chromosome 18q21.1 and is frequently mutated in secondary AML.

The prognosis of secondary AML is usually poorer than that of *de novo* AML. Secondary AML tends to be refractory to chemotherapy, and has decreased treatment tolerance in patients who have received prior chemotherapy.[28] We could not conclude whether AML in this patient was secondary or *de novo* AML. Our patient was unable to achieve remission of AML and his prognosis was poor.

Conclusion

We hope that this case report will help with recognition of BCOR-CCNB3 fusion-positive sarcoma and treatment planning, and ameliorate outcomes. Further study and long-term follow-up are required to investigate targeted therapy or immunotherapy in these patients.

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Supplement 1: Treatment protocol for Ewing sarcoma [ThaiPOG-EWS-13SR]

Treatment schedule

Wk	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**
Cycle	1	2	3	4	5	6		7	8	9	10	11	12	13	14
Rx	VDC	IE	VDC	IE	VDC	IE	S	VC(R)	IE	VC	IE	VDC	IE	VDC	IE

Chemotherapy

Regimen	**Given dose**	**Drug**	**Desired dose**	**Day**
VDC regimen				
	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Doxorubicin (Doxo)	37.5 mg/m^2/day IV slowly push	1,2
	_____mg	Cyclophosphamide (CTX)	*1200 mg/m^2 IV drip in 1 h	1
	_____mg	Mesna 300 mg/m^2/dose IV drip in 15 min at 0, 3, 6, 9 h of starting CTX		
VC regimen				
	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Cyclophosphamide (CTX)	*1200 mg/m^2 IV drip in 1 h	1
	_____mg	Mesna 300 mg/m^2/dose IV drip in 15 min at 0, 3, 6, 9 h of CTX		
IE regimen				
	_____mg	Ifosfamide*	1800 mg/m^2/day IV drip in 1 h	1–5
	_____mg	Etoposide	100 mg/m^2/day IV drip in 1–2 h	1–5
	_____mg	Mesna 450 mg/m^2/dose IV drip in 15 min at 0, 3, 6, 9 h of ifosfamide		

- Give chemotherapy every 2 weeks when absolute neutrophil count (ANC) >750 and platelet count >75,000, and 24 h after the last granulocyte colony-stimulating factor (G-CSF) dose
- Blood for liver function test, BUN, Creatinine or before each course
- If body weight (BW) <12 kg, calculate chemotherapeutic agent dose per kg [(desired dose/30) x BW]
- Start G-CSF 5 mcg/kg daily at 24–36 h after completion of each cycle of chemotherapy, and continue G-CSF until ANC >750 for 2 consecutive days
- Total cumulative dose of doxorubicin is 375 mg/m^2, consult cardiologist at end of protocol for evaluation of cardiac function
- Give appropriate antiemetic drugs
- Surgery at week 12
- Radiotherapy start at week 14
    - No evidence of microscopic residual disease: no radiotherapy
    - Microscopic residual disease: 45 Gy to the original disease site plus a 5.4 Gy boost (1.8–2 Gy/fraction)
    - Gross residual disease: 45 Gy to the original disease site plus a 10.8 Gy boost (1.8–2 Gy/fraction)
    - Metastatic disease: palliative radiotherapy for metastatic site and radiotherapy to primary site depending on surgical margin