Detection of BCOR gene rearrangement in Ewing-like sarcoma: an important diagnostic tool

Lan Li¹, Ming Zhang¹, Shaoyu Chen², Xiaoqi Sun¹, Hairong Xu³, Lina Li², Tingting Zhang¹, Xiaoyuan Huang¹, Hongtao Ye⁴,⁵*, and Yi Ding¹***

Abstract

**Background:** BCOR-CCNB3 sarcoma (BCS) is a group of undifferentiated small round cell sarcomas harboring the BCOR gene rearrangement which shares morphology with the Ewing sarcoma family as well as other malignant round blue cell tumors, thus making them difficult to diagnose. The aim of this study was to explore the role of molecular techniques in the diagnosis of BCS.

**Methods:** Twenty-three cases of EWSR1 rearrangement-negative undifferentiated small round cell sarcomas (Ewing-like sarcoma) were analyzed for the presence of BCOR gene rearrangement by Fluorescence in situ hybridization (FISH) and Reverse Transcription -Polymerase Chain Reaction (RT-PCR). The clinicopathological features of the positive cases were also reviewed. Fifteen additional cases were used as negative controls.

**Results:** Eight cases were found with BCOR gene rearrangement by FISH and reappraised as BCS. The patients ranged in age from 8 to 20 years old, with a male predominance (M:F = 6:2). All tumors were located in the lower extremities. The tumor locations were more common in bone (n = 6) than deep soft tissue (n = 2). Histologically, 7 of 8 tumors were predominately composed of spindle or ovoid cells. The tumor cells were usually arranged in solid hypercellular sheets without a distinct architectural pattern. IHC showed expression of TLE1 (100%), CCNB3 (88%), BCOR (71%). RT-PCR for BCOR-CCNB3 fusion transcript was positive in 7 of 8 cases. Pre-operative chemotherapy resulted in eradication of tumors in 5 patients after a follow-up of 7 to 42 months.

**Conclusions:** Efficient diagnosis of BCOR rearranged sarcomas is achieved by the using a combination of FISH and RT-PCR assays.

**Keywords:** Undifferentiated small round cell sarcoma, BCOR, FISH, RT-PCR

* Correspondence: hongtao.ye@nhs.net; jst_blk@126.com
† Hongtao Ye and Yi Ding are jointly directed and contributed equally to this research.
*Department of Histopathology, Royal National Orthopaedic Hospital, Stanmore, UK
¹Department of Pathology, Beijing Jishuitan Hospital, The Fourth Medical College of Peking University, Beijing, People’s Republic of China

Full list of author information is available at the end of the article

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background

BCOR-CCNB3 sarcomas (BCS) were first identified in 2012 from a series of undifferentiated round cell sarcomas lacking known genetic alterations such as EWSR1 gene rearrangement [1]. Recently, several studies have demonstrated that similar to the epidemiology of Ewing sarcoma, BCS occurs predominantly in adolescents and young adults [2–7]. Although tumors harboring the BCOR-CCNB3 fusion appear to share some clinical and morphological overlap with the Ewing family of tumors, sequencing analysis has shown that the rearrangement involves a paracentric inversion on the short arm of chromosome X, resulting in the fusion of two genes BCOR and CCNB3 and resulting in the expression of CCNB3. Moreover, by gene expression profiling, BCS appear distinct from Ewing sarcoma (ES) [2]. We investigated the prevalence of the BCOR-CCNB3 fusion in pediatric and adult undifferentiated small round cell sarcomas, using a combination of FISH and RT-PCR and report on the clinical and histopathological features of eight patients with sarcomas harboring this fusion gene.

Methods

Specimens

Twenty-three cases of EWSR1 rearrangement-negative undifferentiated small round cell sarcomas (Ewing-like sarcoma) were analyzed for the presence of the BCOR gene rearrangement. All of the cases were retrieved from the archives of Department of Pathology, Beijing Jishuitan Hospital, The Fourth Medical College of Peking University. All paraffin blocks selected were rich of tumors without decalcification. Fifteen cases including 7 PNET/Ewing sarcomas, 5 synovial sarcomas, 1 osteosarcoma and 2 malignant peripheral nerve sheath tumors were selected as negative controls. Representative paraffin-embedded material and haematoxylin and eosin-stained slides were reviewed for all cases. The study complied with local ethical standards. The study protocol was approved by the ethics committee at the Beijing Jishuitan Hospital, China.

Mitotic figures were counted in 10 consecutive high-power fields (1 HPF = 0.238 mm²) in highly proliferative ‘hot spot’ areas.

Immunohistochemistry (IHC)

Immunohistochemistry was performed using antibodies to CD99 (O13, monoclonal, ready to use, Roche, Basel, Switzerland), Fli-1 (G146–22, monoclonal, 1:50; OriGene, Maryland, United States), CCNB3 (polyclonal, 1:300; Sigma-Aldrich, St. Louis, MO), BCOR (C-10, monoclonal, 1:100; OriGene, Maryland, United States), DUX4 (P4H2, monoclonal, 1:250; Thermo Fisher Scientific, Massachusetts, United States), NKX2.2 (EP336, monoclonal, 1:100; OriGene, Maryland, United States), WT-1 (6F-H2, monoclonal, 1:100; Dako, Glostrup, Denmark), calretinin (polyclonal, 1:100; OriGene, Maryland, United States), MUC4 (8G7, monoclonal, 1:50; OriGene, Maryland, United States), TLE1 (UMAB25, monoclonal, 1:100; OriGene, Maryland, United States), EMA (GP1.4, monoclonal, 1:100; OriGene, Maryland, United States). Diaminobenzidine was used as a chromogen in all reactions. Positive and negative controls were included in each immunohistochemistry run.

Fluorescence in situ hybridization (FISH)

FISH was performed using the commercially available BCOR dual color break apart probe (Guang Zhou LBP Medicine Science and Technology, Guangzhou, China). In brief, deparaffinized sections were digested with pepsin at 85°C for 5 mins. Subsequently, the tissue sections and BCOR break apart probe were co-denatured at 85°C for 5 mins and hybridized overnight at 37°C. Following hybridization, washing was performed. Slides were then counterstained with 4′,6-diamidino-2-phenylindole (DAPI) and mounted with coverslips. A positive result was obtained when at least 10% of the nuclei analyzed revealed a break apart signal on counting a minimum of 100 consecutive non-overlapping nuclei. Unlike other typical positive patterns of break apart signals, the distance between the green and red signal for BCOR rearranged case is a small gap reflective of the underlying paracentric inversion and is usually less than the diameter of two signals. BCOR signals were scored by independently two experienced pathologists.

RNA extraction and reverse transcription (RT)

Two 10 µm or 5–10 µm sections were cut from resection or biopsy specimen blocks, respectively, and placed into Eppendorf tubes. RNA was extracted from paraffin-embedded samples using FFPE RNA Isolation Kit (ThermoFisher Scientific, USA). Between 5 and 8 µl of the resulting RNA samples were reverse transcribed using Superscript III First-Strand Synthesis kit (ThermoFisher Scientific, USA) according to the manufacturer’s instructions.

Conventional polymerase chain reaction (PCR) and sanger sequencing

PCR amplification was performed on duplicate samples of 1 µl aliquots of cDNA with HotStarTaq DNA polymerase (Qiagen, Valencia, USA) using primers (BCOR exon 15 – GGGAGCTTATGATCGTGTCAGA and CCNB3 exon 5 – GTTGGTTTCTCCATAATGTTTGTTT) in order to generate a 171-bp product [3]. A touchdown protocol was used with cycling parameters as follows: 7 min at 95°C followed by 45 s at 94°C, 45 s at 66°C, 1 min 30s at 72°C which was followed by reducing the annealing temperature by 1°C each cycle to 57°C (10 cycles), followed by 30 cycles at 56°C and finally 5 min at...
72 °C. Products were separated through an 8% polyacrylamide gel, stained with ethidium bromide and visualized under UV illumination. The house-keeping gene G6PD was used for RNA quality control. Direct Sanger sequencing was performed using BigDye Terminator v3.1 chemistry (Life Technologies) on positive cases.

Results
Clinical and histological features
Twenty-three cases of EWSR1 rearrangement-negative undifferentiated small round cell sarcomas were analyzed by FISH and RT-PCR respectively. Eight of 23 cases were positive for BCOR gene rearrangement by FISH analysis (Table 1). Among these 8 cases, 3 tumors were needle core biopsies and 5 were resection samples. The percentage of samples with break-apart signals in this study varied from 21 to 53% of the cells in the cases in which BCOR gene rearrangement was found. These cases are considered as BCOR-rearranged sarcoma. Seven of 8 cases carrying BCOR gene rearrangement were positive for BCOR-CCNB3 fusion transcript by RT-PCR. Patients with these tumors presented between the ages of 8 and 20, the mean age being 12 years and the tumors were more prevalent in males than females (6 males and 2 females). All primary tumors were located in lower extremities (Table 1). Radiological review showed that most cases presented as lytic masses with irregular margins on plain X-rays (Fig. 1a).

Macroscopic findings showed grey, brown soft tumor with medium texture, focally translucent in four cases (case 1, 2, 4 and 8). Some areas had a gelatinous appearance (Fig. 1b). Soft tissues infiltration around the tumors were found in 6 of 8 cases.

Histological assessment revealed that the tumors were composed of monomorphic spindle or ovoid cells often arranged in solid hypercellular sheets without a distinct architectural pattern (Fig. 1c) and less often in a vague whirling pattern (Fig. 1d). The tumors showed variable cellularity and the nuclei demonstrated a finely dispersed chromatin pattern (Fig. 1e), and hypocellular myxoid areas focally (Fig. 1f). Case 7 was composed of predominantly primitive round cells (Fig. 1g). Most of the tumors showed a rich capillary network which was a notable characteristic (Fig. 1g). Case 5 demonstrated a striking perivascular arrangement and cell clustering (Fig. 1h). Only one patient (case 1) showed recurrent and metastatic tumors; both the primary and recurrent specimens were available for analysis. When compared with the primary tumor, the recurrent sarcoma showed a higher degree of pleomorphism with large, highly atypical spindle cells within a fibrotic matrix and hemorrhage and necrosis. Four of the patients (case 2, 4, 5 and 8) that received chemotherapy showed a significant response to chemotherapy (Fig. 2). Two tumors (case 2 and 8) showed a vascular tumor-like appearance (Fig. 2c). Across all 8 cases, the mitotic activity per 10 HPF ranged from 1 to 11 (mean 8).

### Table 1 Clinicopathologic factors in BCS patients

| Case | Age/ Sex | Location | Size (cm) | BCR FISH positive | BCOR-CCNB3 RT-PCR positive | neoadjuvant chemotherapy | surgery | Chemotherapy/Radiation (after surgery) | Follow-up (months) | Recurrence and Metastasis (Site) |
|------|----------|----------|-----------|-------------------|---------------------------|--------------------------|---------|----------------------------------------|-------------------|----------------------------------|
| 1    | 14/M     | Calcaneus | 5         | Yes               | Yes<sup>a</sup>           | Yes*                     | Chemotherapy<sup>a</sup> | 46(DOD) | Recurrence & metastasis to lung       |
| 2    | 20/M     | Femoral shaft | 12   | Yes               | Yes<sup>b</sup>           | Yes*                     | Chemotherapy<sup>a</sup> | 40(NED) | No                                |
| 3    | 8/M      | Fibula   | NA        | Yes                | Yes                     | No                       | Chemotherapy<sup>a</sup> + Radiation<sup>a</sup> | 42(NED) | No                                |
| 4    | 10/M     | Proximal tibia | 16   | Yes               | Yes<sup>c</sup>          | Yes*                     | Chemotherapy<sup>d</sup> | 29(NED) | No                                |
| 5    | 18/M     | Distal femur | NA     | Yes                | Yes<sup>d</sup>          | Yes*                     | Chemotherapy<sup>d</sup> | 22(NED) | No                                |
| 6    | 13/F     | Leg      | NA        | Yes                | Not                     | Yes                     | Chemotherapy<sup>f</sup> | 9(NED)  | No                                |
| 7    | 10/M     | Leg      | NA        | Yes                | No                      | Yes<sup>e</sup>         | ND      | 9(AWD)                             | No                |
| 8    | 11/F     | Proximal femur | 9      | Yes                | Yes<sup>e</sup>          | Yes*                     | Chemotherapy<sup>f</sup> | 7(NED)  | No                                |

<sup>M</sup> male, <sup>F</sup> female, <sup>DOD</sup> dead of disease, <sup>ND</sup> no evidence of disease, <sup>AWD</sup> alive with disease, <sup>NA</sup> not available, <sup>1</sup> chemotherapy was receiving when the article was written, <sup>2</sup> primary and recurrent specimens were available, <sup>a</sup> chemotherapy regimens were Vincristine,Oncovin (VCR),Adriamycin (ADR), Cyclophosphamide (CTX),Ifosfamide (IFO) and Etoposide (VP-16).<sup>3</sup>VP-16 + IFO + Endostar+Methotrexate (MTX) + Cisplatin (DDP) + VCR + ADR + CTX.<sup>4</sup> VCR + ADR + CTX + IFO + MTX.<sup>5</sup> IFO + MTX + DDP + ADR.<sup>6</sup> ADR + MTX + IFO + Apatinib.<sup>7</sup> IFO + VP16 + MTX + DDP + VCR + ADR + CTX. <sup>#</sup> DF40G/20fx
negative control samples revealed the BCOR rearrangement (Fig. 4a, Supplementary Figure 1).

**IHC analysis**
Seven of 8 cases showed protein expression of CCNB3 (88%, 7/8 cases), and showed expression of TLE1 (100%, 8/8 cases), BCOR (71%, 5/7 cases), CD99 (13%, 1/8 cases). Fli-1, DUX4, NKX2.2, WT-1, calretinin, MUC4, EMA were all negative in the 8 cases (Table 2) (Fig. 3). The expression of CCNB3, TLE1, BOCR, CD99, Fli-1, DU4X, NKX2.2, WT-1, calretinin, MUC4 and EMA in the 15 cases of EWSR1 gene rearrangement-negative undifferentiated small round cell sarcomas (Ewing-like sarcoma) and 15 cases of negative controls were included in Table 3.

**Detection of BCOR-CCNB3 fusion transcript by RT-PCR**
Seven of the 8 cases carrying BCOR gene rearrangement by FISH were confirmed to have the BCOR-CCNB3 fusion transcript by RT-PCR. The chimeric transcript joined the exon 15 of BCOR to exon 5 of CCNB3 in all of the positive cases. The remaining 15 cases were negative (Fig. 4b, c).
Treatment and follow-up

All 8 cases had clinical follow-up data. The average follow-up duration of the study group was 38 months (range from 7 to 46 months). All patients with available follow-up presented with localized disease at diagnosis. During the follow-up period, case 1 developed local recurrence and distant metastases to lung. Of the 8 patients, 5 cases (case 1, 2, 4, 5 and 8) received neoadjuvant chemotherapy followed by surgery and chemotherapy. Case 3 received chemotherapy and radiation therapy without surgery. Case 6 was receiving chemotherapy after surgery when the article was written and case 7 was receiving neoadjuvant chemotherapy meanwhile. The chemotherapy regimens used and the dose of radiation therapy adopted were listed in Table 1. Four cases showed significant response to the chemotherapy (>90% necrosis/fibrosis) in the resection specimens (case 2, 4, 5 and 8). The patient (case 1) underwent curettage then the tumor relapsed 3 months later and amputation was adopted, but unfortunately the tumor metastasized to the lung and the patient died 2 years later. Five patients are alive in sustained complete remission (case 2, 3, 4, 5 and 8) after follow-up up to 42 months.

Discussion

In this study, we investigated a series of 23 cases of EWSR1 rearrangement-negative undifferentiated small round cell sarcoma and found 8 cases harboring the BCOR gene rearrangement. BCOR-CCNB3 fusion transcript was detected in seven of 8 cases by RT-PCR. The 8 patients with BCOR gene rearrangement have a strong

| Case | CD99 | Fli-1 | CCNB3 | BCOR | DUX4 | Nkx2.2 | WT-1 | calretinin | MUC4 | TLE1 | EMA |
|------|------|-------|-------|------|------|--------|------|------------|------|------|-----|
| 1    | Negative | Negative | Positive | Positive | Negative | Negative | Negative | Negative | Negative | Positive | Negative |
| 2    | Negative | Negative | Negative | Positive | Negative | Negative | Negative | Negative | Negative | Positive | Negative |
| 3    | Negative | Negative | Positive | NA     | Negative | Negative | Negative | NA       | Positive | NA    | NA   |
| 4    | Positive | Negative | Positive | Negative | Negative | Negative | Negative | Negative | Negative | Positive | Negative |
| 5*   | Negative | NA     | Positive | Negative | Negative | Negative | Negative | NA       | NA     | Positive | Negative |
| 6    | Negative | NA     | Positive | Positive | Negative | Negative | NA     | NA       | NA     | Positive | Negative |
| 7    | Negative | NA     | Positive | Negative | NA     | Negative | NA     | NA       | Negative | Positive | Negative |
| 8*   | Negative | Negative | Positive | Negative | Negative | Negative | NA     | NA       | Negative | Positive | Negative |

*IHC was performed on the specimen after neoadjuvant chemotherapy; NA not available

![Fig. 3 Immunohistochemistry features of BCS. A The tumor cells were CCNB3 positive. B The tumor cells were BCOR positive. C The tumor cells were TLE1 positive. D The tumor cells were CD99 focally positive in the cytoplasm. Immunoperoxidase, original total magnification × 200 (A-D)](image-url)
male predominance (M:F = 6:2) and predilection for children and adolescents. All tumors were located in lower extremities. The tumor locations were more common in bone (n = 6) than deep soft tissues (n = 2). Most of the cases showed predominantly monomorphic ovoid to short spindle cells arranged in intersecting fascicles, reminiscent of synovial sarcoma, with a rich capillary network. Some hypocellular areas were seen with myxoid stroma, consistent with previous reports [1, 4–8].

Since synovial sarcoma, solitary fibrous tumor, malignant peripheral nerve sheath tumor and osteosarcoma are among the potential differential diagnoses of BCOR-rearranged sarcomas, the detection of BCOR gene rearrangement is very important in the diagnostic appraisal of this lesion, particularly in needle core biopsies [9].

BCS as a recently defined genetic entity tumor among undifferentiated small round cell sarcoma. Most of the cases reported in articles were reappraised through a variety of molecular methods and screening from retrospective studies [1, 4–6, 8]. The original diagnoses in some of cases were mis-classified as ES, Ewing-like sarcoma, synovial sarcoma, and small cell osteosarcoma. In our series, three cases (case 1, 2 and 3) were originally diagnosed as Ewing-like sarcoma. Three cases (case 4, 5 and 8) were originally diagnosed as small cell osteosarcoma and received an osteosarcoma chemotherapy protocol. Therefore, accurate detection of BCOR gene rearrangements and other rare translocations are vitally important for appropriate patient management.

The sensitivity and specificity of CCNB3 immunohistochemistry has been discussed recently [1, 3, 4, 10, 11]. Matsuyama et al. [6] argued that the complete sensitivity of CCNB3 immunohistochemistry in some previous studies was based on the screening method using CCNB3 immunohistochemistry [4, 11]. CCNB3 was not...
always expressed in BCS in other studies, especially in post chemotherapeutic or metastatic tumors [3]. BCOR immunohistochemistry is a highly sensitive marker in identifying small round cell sarcomas with BCOR gene rearrangement [12], but another report suggested that BCOR is less specific than CCNB3 for the diagnosis of BCS [6].

Our data showed high sensitivity of TLE1 expression for BCS (8/8, 100%). However, TLE1 expression was by no means specific for BCS, being present in Ewing-like sarcoma (9/15, 60%), Ewing sarcoma (3/7, 43%), malignant peripheral nerve sheath tumors (2/2, 100%) and synovial sarcoma (4/5, 80%). Regarding the specificity of TLE1 expression as a diagnostic marker for synovial sarcoma, published studies of TLE1 expression have shown conflicting results [13, 14]. Foo et al. have shown TLE1 protein expression to be a sensitive and specific marker for synovial sarcomas and can be used to distinguish poorly differentiated synovial sarcoma from histologic mimics [13]. However, Kossemehtetoglu et al. revealed that TLE1 was not only expressed in synovial sarcoma. TLE1 expression was also seen in 53 of 143 (37%) non-synovial sarcoma, such as malignant peripheral nerve sheath tumors, neurofibromas and schwannomas [14].

The specificity and sensitivity of the antibody may be related to the conditions such as tissue fixation, the dilutions of the antibody, the quality and sensitivity of the antibodies themselves as well as the IHC scoring method. Therefore, immunohistochemistry of CCNB3 and BCOR expression may not be sufficient for diagnosis of BCOR-rearranged sarcomas.

In this study, we show that FISH using dual color BCOR break-apart probe is a reliable assay. Because the BCOR-CCNB3 fusion is caused by a paracentric inversion of 2 closely located genes BCOR and CCNB3 on the short arm of chromosome X, it was thought that the two genes were too close (only 10 Mb apart) to be reliably detected by dual color break-apart probes. Therefore, FISH using the 3 color BCOR-CCNB3 fusion assay has been advocated [2]. Our data shows that dual color BCOR break-apart probe could be suitable for the detection of BCOR gene rearrangement. In Matsuyama’s report [6], eight of the 9 cases were confirmed to have BCOR gene rearrangement using dual color BCOR break apart probe.

RT-PCR is a reliable assay to detect BCOR-CCNB3 fusion transcript. The sensitivity and specificity of RT-PCR in our study are 87.5% (7/8) and 100% (15/15), respectively. In one case the BCOR-CCNB3 fusion transcript was not detected by RT-PCR. The possible reason could relate to tumor cellularity as the percentage of the BCOR split cells was relatively low (21%) by the FISH assay. Another possible reason why RT-PCR was less than 100% sensitive is that BCOR may have other fusion partners besides CCNB3, such as BCOR-MAML3 and KMT2D-BCOR [2, 15]. In additional to the fusion transcripts, BCOR internal tandem duplications have been identified [2].

As BCS is rare there is limited clinical outcome data. These tumors were originally classified among ES family of tumors, and as such have been managed with ES-related chemotherapy protocols [2, 16]. Three previous studies have suggested that BCS are chemoresponsive [2, 4, 7]. Cohen-Gogo et al. [7] showed a good histologic response (> 90% necrosis) in 83% (10/12) of the evaluable patients treated mainly with ES chemotherapy. Four of the 6 post chemotherapy resections showed complete response, whereas the remaining 2 had scattered residual tumor cells in Puls’ study [4]. Kao, et al. demonstrated 5 of the 9 patients were good response to chemotherapy with > 90% necrosis and 2 of the 9 patients with 60–90% necrosis [2]. In our study, 4 cases received induced chemotherapy showed a good histologic response (> 90% necrosis). However, 3 patients treated with chemotherapy before surgery were based on protocols for osteosarcoma, and 1 patient treated with protocols for ES. As both the osteosarcoma-based and the ES-based regimens were combination regimens, it is difficult to know which regimen was the one responsible for the definitive response. Controlled prospective studies will be necessary to choose an optimum therapy for BCS.

This study shows that the combination of FISH and RT-PCR to detect BCOR gene rearrangements are reliable assays and should be considered in the diagnostic workup of undifferentiated round cell tumors that are negative for the EWSR1 gene rearrangement.

**Abbreviations**  
BCS: BCOR-CCNB3 sarcoma; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; RT: Reverse Transcription; PCR: Polymerase Chain Reaction; ES: Ewing sarcoma

**Supplementary Information**  
The online version contains supplementary material available at https://doi.org/10.1186/s13000-021-01114-2.

**Additional file 1:** The summary of 38 cases detected by FISH with BCOR break apart probe.

**Acknowledgements**  
The authors are very grateful to the scientists of Guang Zhou LBP Medicine Science and Technology Co., LTD for their technical support. We also thank Mrs. Lei Zhao for collecting our materials.

**Authors’ contributions**  
LL and YD designed the research. LL analysed FISH data, carried out the literature search, generated figures and drafted the manuscript. MZ and XQS performed FISH and IHC analyses. SYC and LNL performed RT-PCR analyses. LL, HRX, TTZ and XYH collected and interpreted pathological and clinical data. HTY interpreted FISH and RT-PCR data and provided critical review of the data and manuscript. YD supervised the study. All authors reviewed the paper and had final approval of the submitted version.
Authors’ information

Not applicable.

Funding

The Capital Characteristic Project of Beijing Science and Technology Project (Z171100000017134).

The Beijing Jishuitan Hospital Nova Program (XKXX201811).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee at the Beijing Jishuitan Hospital, China.

Consent for publication

All patients provided consent for information to be published.

Competing interests

The authors have no conflicts of interest to declare.

Author details

1Department of Pathology, Beijing Jishuitan Hospital, The Fourth Medical College of Peking University, Beijing, People’s Republic of China. 2Guangzhou LBP Medicine Science & Technology Co., Ltd, Guangzhou, People’s Republic of China. 3Department of Orthopedic Oncology Surgery, Beijing Jishuitan Hospital, The Fourth Medical College of Peking University, Beijing, People’s Republic of China. 4Department of Histopathology, Royal National Orthopaedic Hospital, Stanmore, UK. 5Department of Pathology, Affiliated Hospital of Guangxi Medical University, Guangxi, People’s Republic of China.

Received: 23 March 2021 Accepted: 1 June 2021

Published online: 08 June 2021

References

1. Pierron G, Tirode F, Lucchesi C, Reynaud S, Ballet S, Cohen-Gogo S, et al. A new subtype of bone sarcoma defined by BCOR-CCNB3 gene fusion. Nat Genet. 2012;44(6):461–6. https://doi.org/10.1038/ng.1107.
2. Kao YC, Owosho AA, Sung YS, Zhang L, Fujisawa Y, Lee JC, et al. BCOR-CCNB3 fusion positive sarcoma: a clinicopathologic and molecular analysis of 36 cases with comparison to morphologic spectrum and clinical behavior of other round cell sarcomas. Am J Surg Pathol. 2018;42(5):604–15. https://doi.org/10.1097/PAS.0000000000000965.
3. Peters TL, Kumar V, Polikarpadis S, Lin FY, Sarabia SF, Liang Y, et al. BCOR-CCNB3 fusions are frequent in undifferentiated sarcomas of male children. Mod Pathol. 2015;28(4):575–86. https://doi.org/10.1038/modpathol.2014.139.
4. Pulv F, Niblett A, Marland G, Gaston CL, Dousi H, Mangham DC, et al. BCOR-CCNB3 (Ewing-like) sarcoma: a clinicopathologic analysis of 10 cases, in comparison with conventional ES. Am J Surg Pathol. 2014;38(10):1307–18. https://doi.org/10.1097/PAS.0000000000000223.
5. Ludwig K, Alaggio R, Zin A, Peron M, Guzzardo V, Benini S, et al. BCOR-CCNB3 undifferentiated sarcoma-does immunohistochemistry help in the identification? Pediatr Dev Pathol. 2017;20(4):321–9. https://doi.org/10.1057/psdp.201631.
6. Matsuyama A, Shibayama T, Nakashima Y, Kato T, Sakurai T, Minamiguchi S, et al. Screening of BCOR-CCNB3 sarcoma using immunohistochemistry for CCNB3: a clinicopathological report of three pediatric cases. Pathol Int. 2015;65(8):410–4. https://doi.org/10.1111/his.13001.
7. Shiba A, Tomita T, Nakashima Y, Kato T, Sakurai T, Minamiguchi S, et al. Screening of BCOR-CCNB3 sarcoma using immunohistochemistry for CCNB3: a clinicopathological report of three pediatric cases. Pathol Int. 2015;65(9):792–801. https://doi.org/10.1111/his.13189.
8. Rekhi B, Kembhavi P, Mishra SN, Shetty O, Bajpai J, Puri A. Clinicopathologic features of undifferentiated round cell sarcomas of bone & soft tissues: an attempt to unravel the BCOR-CCNB3 & CIC-DUX4-positive sarcomas. Indian J Med Res. 2019;150(6):557–74. https://doi.org/10.4103/ijmr.IJMR_2144_18.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.