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Morphologic Spectrum of BCOR-Expressing Sarcomas: Clinicopathologic Study of 37 Cases

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Abstract: ***Introduction: BCOR (BCL6 co-repressor) sarcomas are a group of undifferentiated small round to spindle cell sarcomas harbouring the BCOR gene rearrangement, which share morphology with other mesenchymal and malignant round blue cell tumours. Aims & Objectives: To study the various morphologic patterns of BCOR-expressing sarcomas in bone and soft tissues. Methods: We collected 37 BCOR-positive cases over a 1-year period for detailed clinical profiles, morphology, and immunohistochemical analysis. Results: Twenty-one (56.7%) cases occurred in males and sixteen (43.2%) in females; the common age group being 11-20 years. The most common site involved was deep soft tissue. Visceral site involvement was seen in three cases. Histopathology predominantly showed spindled cell morphology. BCOR expression is a defining feature of BCS. The other markers frequently expressed alongside BCOR in BCS tumours are TLE1 (56.7%), MIC2 (56.7%), SATB2 (40.5%), NKX2.2 (5.4%), and WT1 (2.7%). Conclusion: We studied 37 cases of BCOR-expressing tumours in bone and soft tissues, highlighting the morphologic and immunohistochemical overlap. It is important to diagnose BCOR sarcomas as it has good prognosis than others, and there is emerging evidence of targeted therapies associated with it.***

Keywords: BCOR, bone and soft tissue, morphologic spectrum, sarcoma

1. Background

BCOR is a gene that encodes for an epigenetic modulator implicated in the determination of cellular lineage commitment and body structural development. As a gene implicated in transcriptional regulation, BCOR is increasingly reported to be mutated in various human cancers, playing a key role in neoplastic transformation or tumour progression. BCOR (BCL6 co-repressor) gene fusion that participates in the polycomb repressive complex (PRC) [1].

BCOR genetic alterations include BCOR-CCNB3, BCOR internal tandem duplication (BCOR-ITD) and BCOR-MAML3. In BCOR-CCNB3, a pericentric inversion on the X chromosome is present, involving these two genes. The fusion leads to the overexpression of the BCOR is a gene that encodes for an epigenetic modulator implicated in the determination of cyclin B3 protein. These tumours predominantly occur in bone or soft tissue of children [1]. This entity was first identified by Pierron et al. in 2012 while analysing a group of undifferentiated round cell sarcomas, especially in translocation-negative 'Ewing-like' sarcomas arising in bone and soft tissue [2][3]. Other translocations, such as BCOR-ITD, are seen in paediatric renal sarcoma, Clear cell sarcoma of the kidney, and endometrial stromal sarcomas, while BCOR-MAML3 is most commonly found in Ewing-like small blue round cell tumour [4].

BCS (BCOR sarcoma) occurs predominantly in adolescents and young adults. Tumours harbouring the *BCOR-CCNB3* fusion appear to share some clinical and morphological overlap with the Ewing family of tumours, CIC- rearranged tumours, synovial sarcomas, osteosarcomas and endometrial stromal sarcomas. Although the use of immunohistochemical markers remains a more practical approach for screening and supporting the diagnosis, only a handful of antibodies are available to help differentiate them from other tumours with undifferentiated morphology [5].

Histologically, BCS showed a spectrum of morphologies ranging from round to spindle cells, with variable cellularity, monomorphic nuclei and a fine chromatin pattern, a delicate capillary network, and varying amounts of myxoid or collagenous stroma. Studies reveal that BCOR-rearranged sarcomas have a treatment profile similar to that of the Ewing family of tumours and a better prognosis than CIC-DUX-associated tumours [2].

The diagnostic workup of BCOR-rearranged sarcomas typically encompasses FISH, RNA sequencing, RT-PCR, and IHC. On immunohistochemical evaluation, BCOR-expressing sarcomas demonstrate strong diffuse nuclear staining, reflecting the protein's role as a transcriptional corepressor of BCL6 that mediates gene silencing via recruitment of the non-canonical polycomb repressive complex 1 (PRC1) [2][3]. This robust nuclear immunoreactivity serves as a reliable indicator across all molecular subtypes of BCOR rearrangement, including BCOR-CCNB3, BCOR-ITD, and BCOR-MAML3. [2][3][5][6].

2. Materials and Methods

Cases of soft tissue and bone diagnosed by IHC as BCS over a 1-year period (i.e., from January 2020 to February 2021) were retrieved from our lab, the Centre for Oncopathology, Wadala, Mumbai. Representative Haematoxylin- and eosin-stained slides, along with immunohistochemical results, were reviewed for all cases. All IHC was done on the Dako platform. Representative 4-um-thick sections of the diagnostic biopsy and recurrent specimens of the positive cases were stained with a rabbit polyclonal antibody to

CCNB3 (clone C10; Santa Cruz) at a 1:25 dilution. Cases without available materials were excluded. Parameters such as age, sex, site, morphologic patterns, stromal component, mitotic activity, degree of necrosis, and immunohistochemistry (IHC) panels including BCOR, SATB2, TLE1, CD99, NKX2.2, and WT1 were analysed. The BCOR case, which showed strong nuclear positivity were read as a positive case. The clinical information was obtained from the referral notes and also through discussions with the referring doctor. Formal written consent was not required, with a waiver by the appropriate IRB and/or national research ethics committee.

3. Results

The patients' ages ranged from 1 month to 60 years old, with the most common age group being 11-20 years; with male predominance (M: F=1.3:1). The tumour locations were slightly more common in deep soft tissue (n=18) than bone (n=16) and other visceral sites (n=03) cases. The visceral sites include liver (n=1), right spermatic cord (n=1) and ovary (n=1).

Out of the total 37 cases, 43.2% (16 of 37) predominantly showed spindle or ovoid cells, rest 40.5% (15 of 37) had round cell morphology, and 16.2% (6 of 37) cases showed epithelioid morphology, respectively. The spindle cell population in our study was monomorphic, with medium-to-high cellularity and ovoid-to-elongated nuclei with a fine chromatin pattern. The round cell tumour was commonly arranged in solid hypercellular sheets, nests, occasional rosettes and a few without a distinct architectural pattern; scant cytoplasm and monomorphic nuclei with fine chromatin, indistinct nucleoli, and smooth nuclear contours. Most of the tumours showed a rich capillary network with myxoid, chondroid, and osteoid matrix. Necrosis, either focal or geographic, was seen in 37.8% (14/37) of cases, and mitotic activity ranged from low to brisk activity.

The BCOR expression is a defining feature of BCS. The other markers frequently expressed in conjunction with BCOR in BCS tumours are TLE1 (56.7%), followed by MIC2 (56.7%), SATB2 (40.5%), NKX2.2 (5.4%) and WT1 (2.7%), respectively. The other positive IHC stains were Cyclin D1 (5 cases) and EMA (focal positivity, 5 cases). INI1 and BRG1were retained in 10 and 4 cases, respectively.

4. Discussion

BCOR (BCL-6 interacting co-repressor) is a transcriptional coregulator gene expressed across a wide range of human tissues, including those where BCL6-expressing mature B cells are found; however, BCOR protein expression in adult human tissues is largely unknown [5]. Most of the cases reported in articles were reappraised through a variety of molecular methods and screening from retrospective studies. Both the morphology and histopathology of BCOR-expressing sarcomas pose a formidable challenge owing to their extensive histopathological overlap, as their differential diagnosis includes Ewing sarcomas, CIC-DUX4 sarcomas, synovial sarcoma, endometrial stromal sarcoma, and osteosarcoma. It is therefore imperative that molecular pathological investigation be incorporated into the diagnostic workup.[6][7]

In this study, we examined a cohort of 37 BCOR-positive tumours for their morphologic characteristics and IHC staining. Our results confirm the observation published in literature; the male predominance and predilection for older children; The adolescents as the most commonly affected population, i.e. 11-20 (32.4%) years [4] [5] [6] [8] [9] [10] [11] [12]. In contrast to a few studies found in the literature, our cohort reveals a preference for soft tissue (48.6%). Thigh mass lesions were the prevailing sites among soft tissue tumours, followed by gluteal, retroperitoneal, paraspinal, right temporal, right chest wall, right nasal mass, right supraglottic, abdominal and orbital sites. In the bone, the femur was the predominant site. Two of the cases studied in bone showed metastasis to the liver and to the bronchus, from a known primary in the fibula (malignant mesenchymal neoplasm) and a known primary in the mandible (mandibular osteosarcoma), respectively.

Among the two visceral sites discussed, one case was seen in the liver with multiple lymphadenopathies and lung nodules diagnosed as an undifferentiated BCOR expressing tumour, and the other was an ovarian mass which was morphologically diagnosed as endometrial stromal sarcoma (Figure 1). [5]

Another 2 cases of BCOR-expressing sarcomas in the right spermatic cord and left supraglottic region were identified in the present study; these are rare, with no case reports in the literature. A Case series by Iarfarate et al. showed a spermatic cord mass diagnosed as an undifferentiated sarcoma, but BCOR IHC was not done. [13]

In this case series, the predominant pattern was spindle cells arranged in intersecting fascicles and sheets, followed by round and epithelioid cell morphology, respectively. Peter T L et al. reported spindle cell morphology in their study [4]; the rest showed predominantly round-cell morphology [3][5][6][8][10].

Our 37 cases were all BCOR-positive by IHC, with TLE1 (20/30), CD99 (17/30), and SATB2 (16/29) positive in the majority. A few of the cases also showed positivity for NKX2.2 (5/31) and WT1 (1/22), compared with various other studies in the literature [6][8]. Many of the bone tumours were positive for TLE1 and SATB2, thus simulating synovial and small-cell osteosarcoma [11] (Figure 2). One of the bone tumours was diagnosed as Ewing's both clinically and morphologically, but was CD99- and NKX2.2-negative and reclassified as BCOR-positive after IHC (Figure 3). Prior investigations have documented that BCOR-expressing tumours most commonly demonstrated immunoreactivity for SATB2 and Cyclin D1 [2][3][4][5]. However, in the present study, the majority of cases were focal or dim-positive for TLE1, Mic2, and SATB2; therefore, strong BCOR positivity should be regarded as the sole marker for BCS [2][3][5][6]. Although histology and IHCs are helpful, the gold standard is molecular testing and cytogenetic studies, which were not performed in our cases. A study by Kao YC et al. highlights that BCOR IHC can be used in a complementary manner to molecular testing [5].

The importance of identifying BCOR sarcomas lies in the fact that these tumours have a broad cytomorphological spectrum, but have a distinct immunoprofile. The therapeutic management parallels that for Ewing's family of tumours, but the literature search also reveals that BCOR has its own targeted therapy [7]. Some of the studies also suggest that non-Ewing sarcoma protocols are a much safer option for BCOR-rearranged sarcomas [7]. Also, these tumours have a more favourable prognosis than some sarcomas, such as CIC-DUX4-rearranged sarcomas [2].

The limitations in this case series were that BCOR-expressing sarcomas have a wide spectrum of cytomorphology. Also, no molecular workup for further classification was available.

5. Conclusion

We studied 37 cases of BCOR-expressing tumours in bone and soft tissues, highlighting the morphologic and immunohistochemical overlap with other primitive round- and spindle-cell sarcomas. Clinical correlation, distinct morphology, and strong nuclear positivity on BCOR IHC are helpful for diagnosis. The literature search shows a correlation between BCOR IHC expression and the rearrangements, i.e., BCOR-CCNB3, BCOR-ITD, and BCOR-MAML3. It is of paramount importance to differentiate BCOR sarcomas from other sarcomas, as they carry a favourable prognosis, and there is a growing body of evidence supporting targeted therapies.

Author's Contribution

All authors contributed equally in the study and revised the paper, drafted the manuscript, collected and interpreted the data, and participated in planning and revising the manuscript. All the authors read and approved the final manuscript. No financial assistance taken.

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Figures

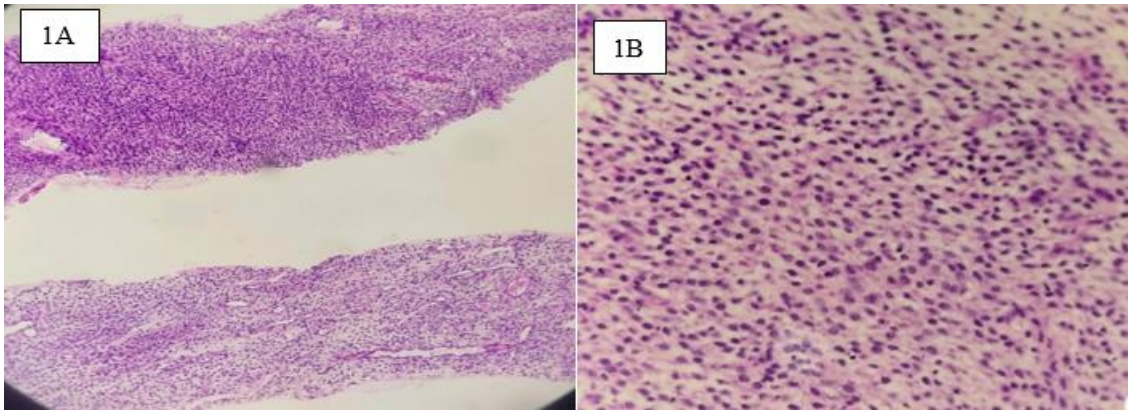

Figure 1: 58/F, Adnexal mass showing sheets of round cells with interspersed thin blood vessels. A-10X view, B-40X view.

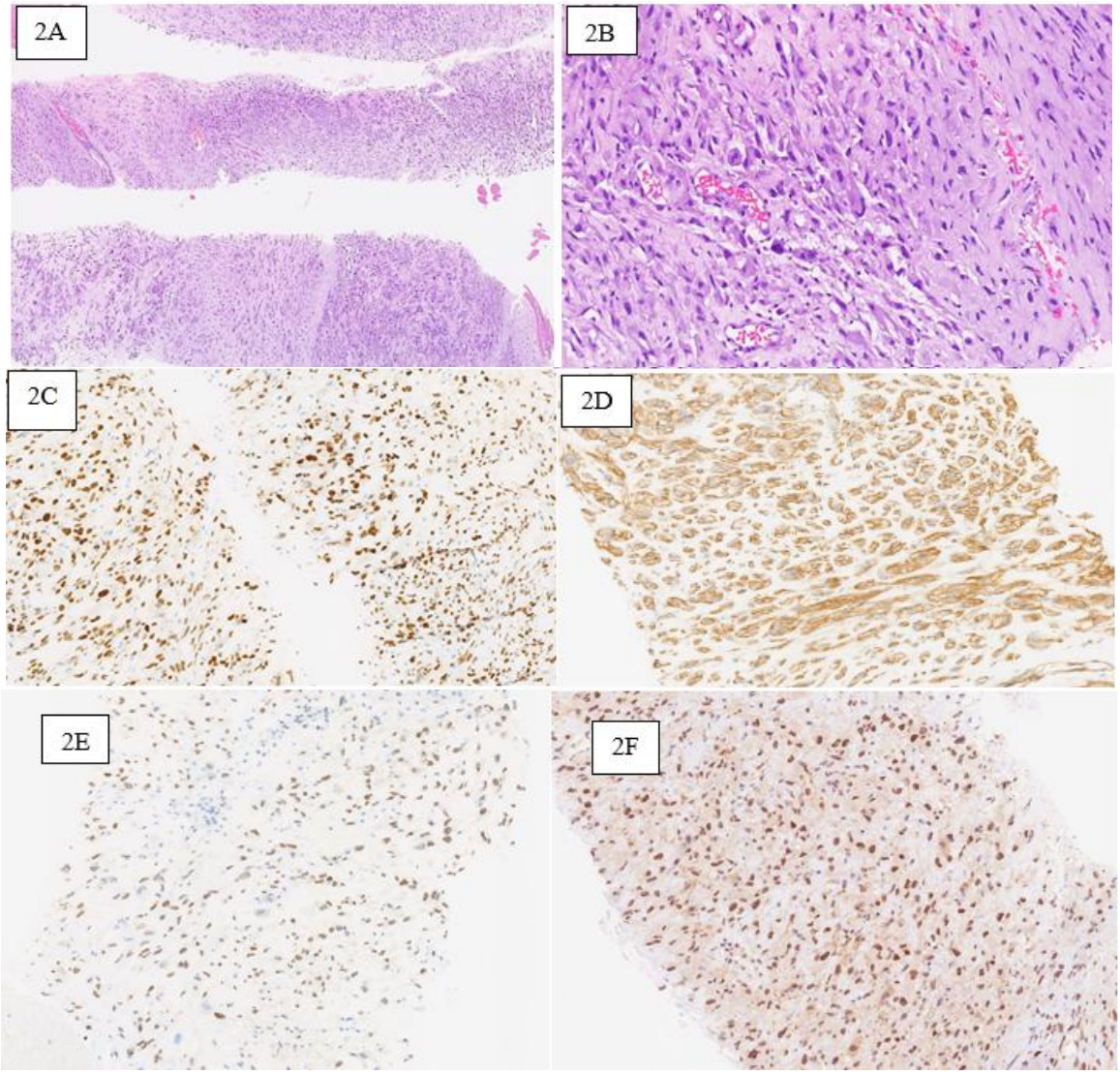

Figure 2a: 14 /F, femoral mid diaphysis, clinically? ES; Pleomorphic spindle -stellate, loose hyalinized stroma, occasional cell with rhabdoid morphology. 10X view,
Figure 2B: 40X view
Figure 2C, 2D, 2E and 2F: Showing BCOR, CD99, TLE1 and SATB2 positivity respectively.

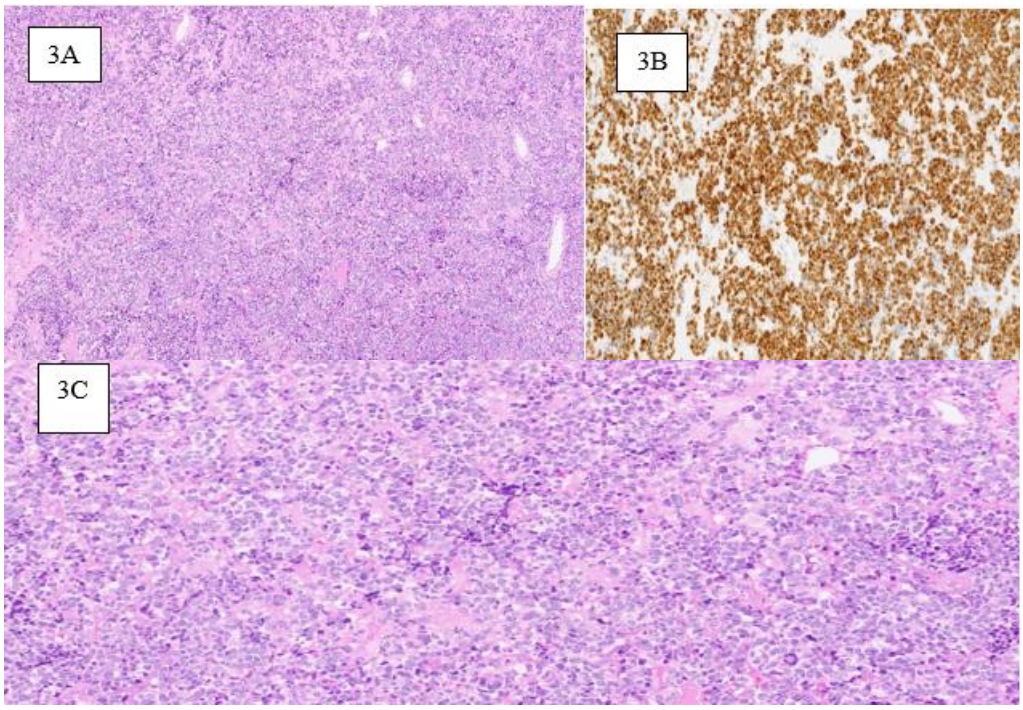

Figure 3: 27/M, patellar tumour showing round cell morphology in sheets, nests and occasional rosettes. Background showing hyalinized stroma. A- 10X view, B- 40X view, C- BCOR positive tumour cells.