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Case of large high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* presenting as Primary bone marrow Lymphoma

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ABSTRACT : Diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* rearrangements in the new WHO classification of hematolymphoid neoplasm are aggressive B-cell lymphoma associated with *MYC* and *BCL2* rearrangements. This designation is an umbrella term; in practice cases are classified as DLBCL or HGBL based on morphologic findings in addition to gene rearrangement data. They were previously known as double hit lymphoma. We present a case of Diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* rearrangements without lymph node involvement involving primarily bone marrow. Primary bone marrow involvement without lymph node makes the diagnosis challenging in setting with limited resources and financial constraints. Immunohistochemistry was used to clinch the diagnosis

KEYWORDS : DLBCL, high-grade B-cell lymphoma (HGBL), MYC, *BCL2*

I. INTRODUCTION

Diffuse large B cell lymphoma is defined morphologically by lymphoma consisting of medium to large B cells with diffuse growth pattern. In the recent updated WHO classification of Hematolymphoid tumors 5th edition there are 17 entities of Large B cell lymphoma outside DLBCL-NOS which are grouped according to genetic, clinical or site specific (extra nodal) origin.[1] The present case has large or intermediate cells therefore morphologically designated as DLBCL. The Immunohistochemistry analysis showed MYC and bcl2 positivity making further categorization as HGBCL (High grade B cell lymphoma) with MYC & bcl2 rearrangement or DLBCL with MYC & BCL2 arrangement. A 64 year male presented in Medicine department of a tertiary care hospital with complaints of fever with chills since three days, fatigue , generalized weakness & shortness of breath since 15 days.

A 64 year old male presented with complaints of fever, shortness of breath and generalized weakness,. The physical examination showed hepatosplenomegaly and left axillary lymphadeopathy. Ultrasonography abdomen showed hepatosplenomegaly with enlarged periportal & peripancreatic nodes. The personal history was insignificant with patient being non alcoholic and non smoker.

The laboratory investigations revealed-BUN- 15 mg/dl, Creatinine -0.8 mg /dl, Sodium 139 m mol/litre, potassium 4.0 m mol/liter, chloride 98 m mol/lit, glucose 100 mg/dl, SGOT- 91U/L,SGPT 53 U/L, total Bilirubin 0.6 mg/dl, Direct Bilirubin-0.2 mg/dl. An automated complete blood count (CBC) demonstrated Hemoglobin- 71 g/L (reference range 130-170 g/L), white blood cell count 5.6 x 10 3 /L (reference range 4-10 x 10 3 /L) Platelet count 80 x 10 6/L (reference range 150-450 x 10 9/L) , with few atypical cells in peripheral blood film. Hepatitis B virus DNS was positive. Test for HIV 1 & 2, Hepatitis C viral serology were non reactive. Malarial smears and rapid malarial antigen test were negative. Routine urine examination did not detect any abnormality. The bone marrow aspirate was dry tap. Bone marrow biopsy was hypercellular with interstitial & nodular aggregates of atypical medium to large lymphoid cells with vesicular nuclei and prominent nucleoli with scant cytoplasm. The erythroid and myeloid series were normal whereas megakaryocytes were increased in number with normal morphology (Fig-1). The picture was suggestive of lymphoma, Non Hodgkins type. Immunohistochemistry of bone marrow biopsy showed positivity for MUM-1 (B cell lymphoma) , C-MYC, CD 5- Weak (T cell marker, Mantle cell marker, SLL), LEF-1- Weak (T cell marker, SLL), CD138 (Plasma cell marker , interstitial), CD 20, CD 79 a (B cell marker) & high Ki 67 index. It was negative for CD3 (T cell marker) , CD 10(Follicular cell marker), Cyclin D1(Mantle cell lymphoma marker) , CD 23(SLL Marker) , CD 34 (Acute leukemia marker) , CD 30 (Classic Hodgkins lymphoma marker) and CD 117 (immature myeloid marker) (Fig -2, Fig-3) . The left axillary lymph node excision biopsy showed non specific reactive hyperplasia.

A diagnosis of HGBCL with MYC/ BCL2 was made. The IHC was performed in the present case but genetic studies could not be done due to financial constraints as mandated by revised classification of hemato lymphoid tumors.

II. Discussion

Aggressive B cell lymphomas primary to bone marrow are aggressive tumors posing diagnostic challenge to pathologists & hematologists to the extent that the topic was chosen for the bone marrow workshop of 19th meeting of the European Association for hematopathology/ society of hematopathology (EAHP/ SH) which took place in Edinburg in September 2018.[2]Most of primary bone marrow lymphoma are B cell NHL among which DLBCL accounts for majority of patients. Primary bone marrow lymphomas principally arise in bone marrow without any lymph node involvement. The criteria for diagnosis of Primary bone marrow lymphoma are as follows [3] :

i. isolated bone marrow infiltration (regardless of peripheral blood involvement);
ii. no evidence of lymph node, spleen, liver, or other extra bone marrow involvement on physical examination or imaging studies;
iii. absence of localized bone tumors;
iv. absence of bone trabeculae destruction in the bone marrow biopsy; and
v. lymphoma, mantle cell lymphoma, splenic marginal zone lymphoma, hairy-cell leukemia, Burkitt lymphoma (BL), and acute lymphoblastic leukemia exclusion of leukemia/lymphoma, such as chronic lymphocytic leukemia/small lymphocytic lymphoma, prolymphocytic leukemia, lymphoplasmacytic lymphoma.

The group of large B cell lymphoma consist of spectrum of tumors of varying clinical, morphological and genetic features with Diffuse Large B cell Lymphoma (DLBCL) NOS as largest entity. In the latest WHO classification of hematolymphoid tumor classification , 5th edition it is emphasized that Large B cell lymphoma that do not meet criteria for diagnosis for more specific entity are classified as DLBCL-NOS. [4]The new edition recognizes 17 specific entities as Large B cell Lymphoma outside DLBCL-NOS according to genetic, nodal site and clinical context. The nomenclature doesn't rely on growth pattern that is needed for making diagnosis. HGBCL with MYC and BCL2 and or BCL6 rearrangement has been restricted to those lymphomas with MYC & BCL2 arrangements.

DLBCL/HGBCL- MYC & bcl2 is an aggressive mature B cell lymphoma presenting as advanced disease with 30-80% presenting as nodal disease.[5] The growth pattern is diffuse and tumor comprise of large to intermediate cells with variable mitotic figures – typical DLBCL morphology. There are some cases that have blastoid morphology, round cells, fine chromatin with small nucleoli & scanty cytoplasm. A third morphological variant is an intermediate one with DLBCL/ Burkitt lymphoma like picture. [6]

DLBCL/ HGBCL MYC/ bcl2 express pan B cell antigens CD 19, CD20, CD 79 a & Pax-5. CD10 positivity is also noted. Most express MYC (78-86%) and bcl2 (90-95%) protein and 71-81% express dual proteins. Ki 67 expression is high.[7]

DLBCL/HGBCL- MYC & bcl2 harbors two oncogenic rearrangements – the first one targeting MYC and second one BCL2.[7] MYC activation drives proliferation and MYC expression leads to apoptotic resistance. They were previously known as double hit lymphoma or triple hit lymphoma in cases with *MYC*, *BCL2* and *BCL6* rearrangements. We present a rare case report of double hit lymphoma without lymph node involvement involving only bone marrow, making the case extremely rare as it further classifies into primary bone marrow lymphoma.

Confronted with the poor prognosis of lymphomas carrying concurrent *MYC*-R and *BCL2* (and/or *BCL6*) rearrangement, the 2016 WHO classification separated these double (DHLs)/triple-hit lymphomas as a formal HGBL category.[8] The WHO advocated that HGBL, NOS, be diagnosed sparingly and "only when the pathologist is truly unable to confidently classify the case as DLBCL or BL.

There is lack of universal acceptance on issue of which cases of DLBCL/HGBCL to undergo MYC translocation analysis. DLBCL/HGBCL- MYC & bcl2 has an aggressive course and immunotherapy with R-CHOP associated with poor outcome. As for the role of dose intensified regimes there is paucity of literature with limited clinical trials as on now.

III. Conclusion

HGBL, NOS, as outlined in the 2016 WHO classification, is a poorly defined and highly heterogeneous entity. Delineation of aggressive high-grade lymphomas that require treatment other than R-CHOP remains a critical priority for research.

Conflict of interest- None
Sources of Funding- Nil

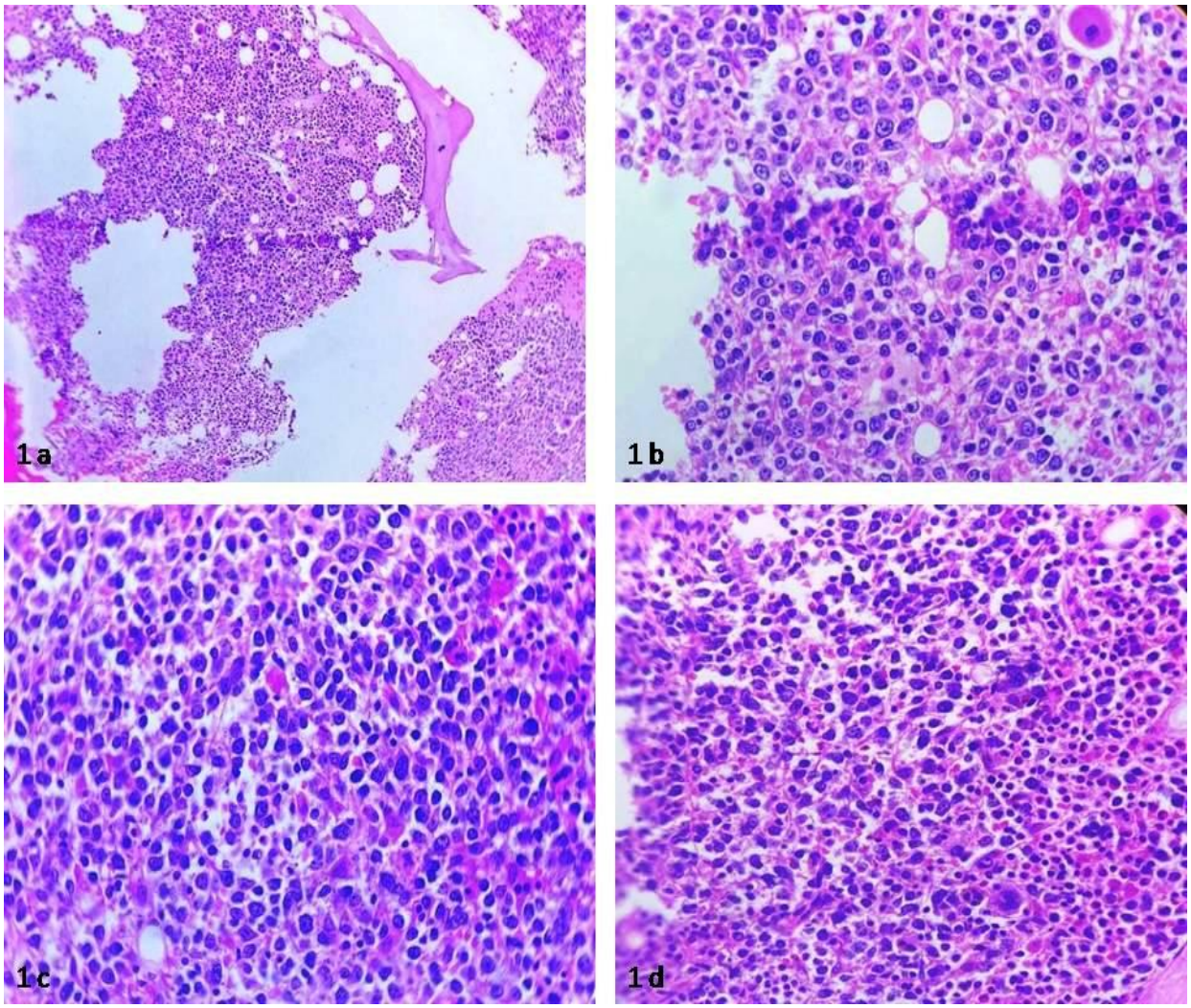

Fig 1 a- Hematoxylin & Eosin section bone marrow biopsy (40x magnification) show medium to large cell population , 1 b-d - Hematoxylin & Eosin section bone marrow biopsy (400x magnification) show atypical medium to large lymphoid cells with vesicular nuclei and prominent nucleoli with scant cytoplasm.

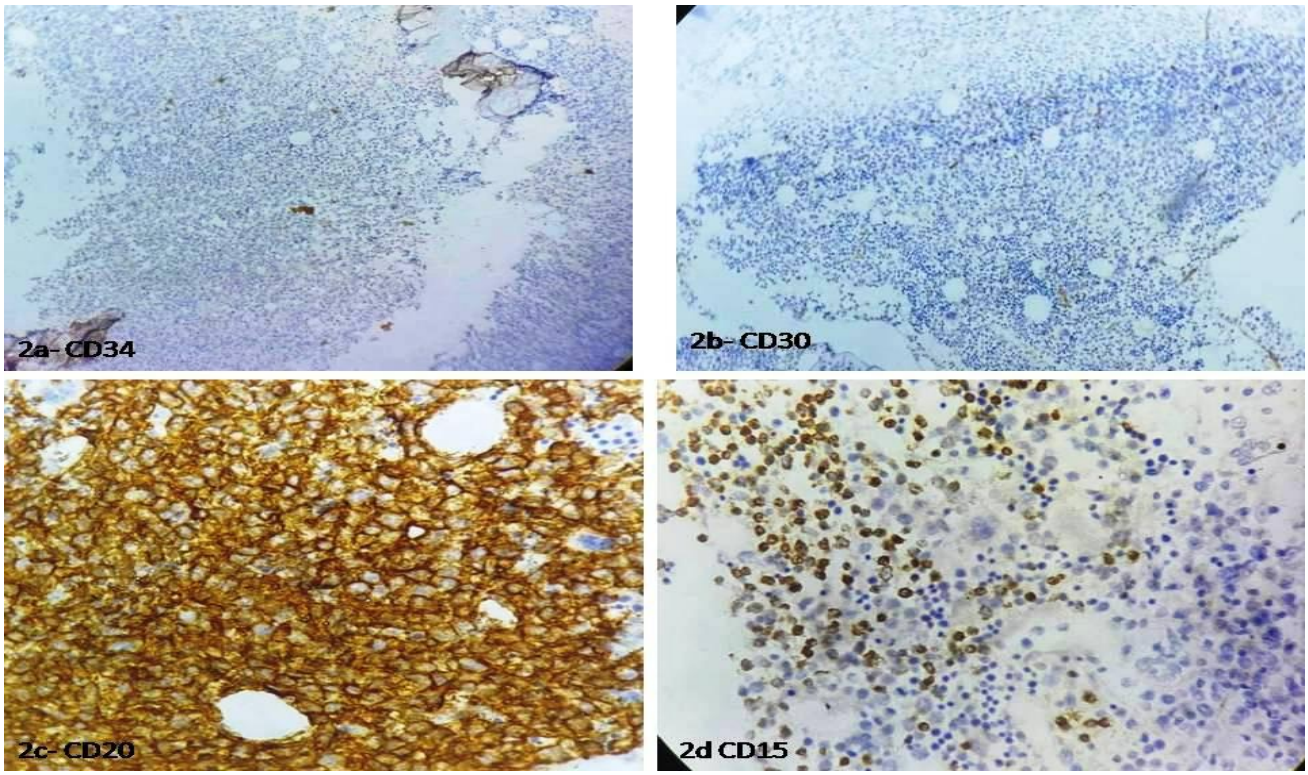

Fig 2- Bone marrow IHC(400x) – 2a- CD34- Negative staining, 2b-CD30- Negative staining , 2c- CD20- Positive staining & 2d- CD15- Positive staining.

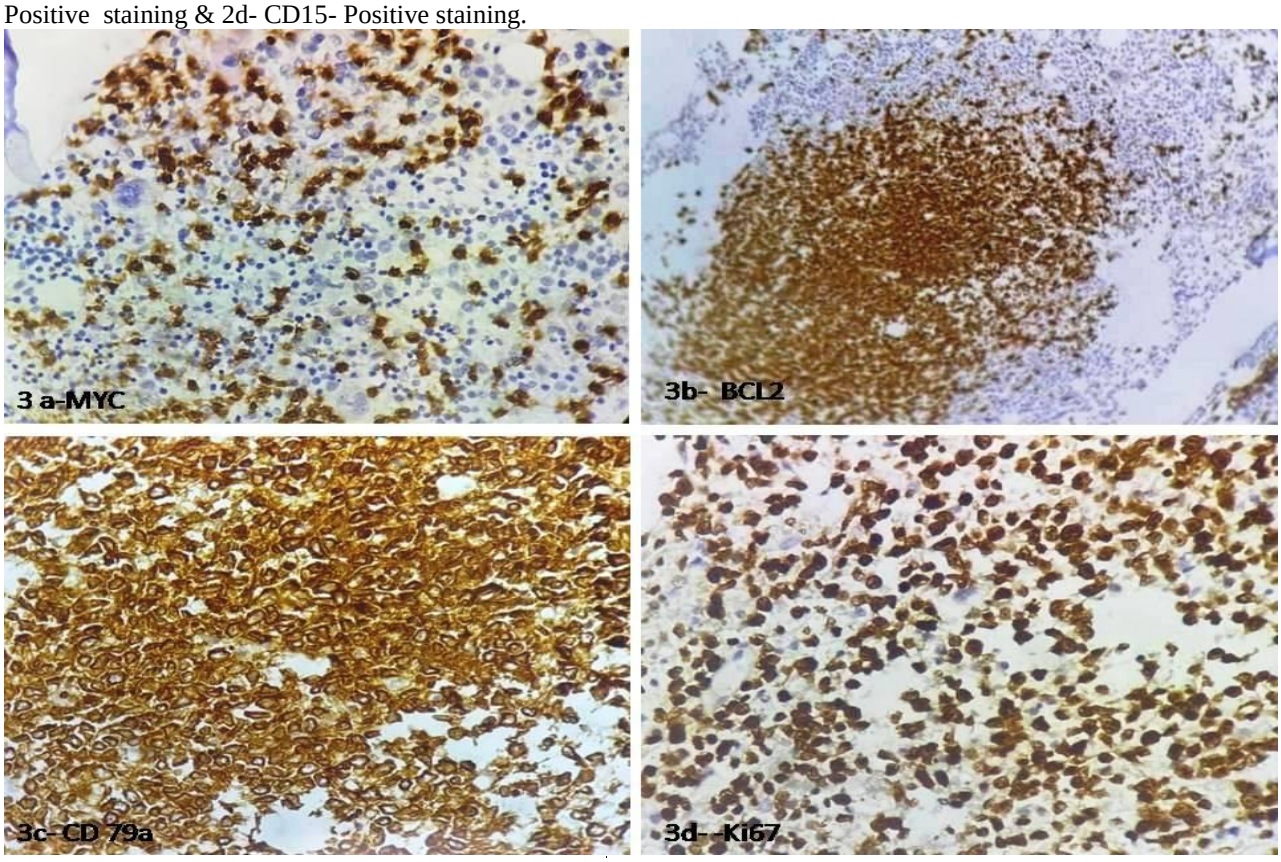

Fig-3 Bone marrow IHC staining (400 x magnification) – 3a- MYC – Positive staining, 3b- BCL2- Positive staining, 3c- CD79a- Positive staining & 3d- Ki67 – Positive (High Ki67 index).

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