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An Unusual Case of High-Grade B-Cell Lymphoma with Both C-Myc and Ccnd1 Rearrangement- "Double-Hit" Lymphoma (Nmrr-18-481-40980)

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Keywords:

Mantle cell lymphoma; Burkitt lymphoma; Double hit lymphoma

1. Background

The 2016 revision of the World Health Organization (WHO) classification for lymphoma has included a new category of lymphoma, separate from diffuse large B-cell lymphoma, termed high-grade B-cell lymphoma with translocations involving *myc* and *bcl-2* or *bcl-6*. These lymphomas, which occur in <10% of cases of diffuse large B-cell lymphoma, have been referred to as double-hit lymphomas or triple-hit lymphomas if all 3 rearrangements are present *[1]*. Mantle cell lymphoma(MCL) is a neoplasm of mature B-lymphocytes with characteristic t (11;14) and subsequent Cyclin D1 overexpression [2] while Burkitt lymphoma(BL) is an aggressive B-cell non-Hodgkin lymphoma that is almost uniformly associated with translocations involving the gene for MYC on chromosome 8 [3]. B-cell lymphoma with CCND1 and 8q24/*c-MYC* abnormalities, referred by some as "double-hit" MCL, is rare. Here we report a case of aggressive B-cell lymphoma with concomitant occurrence of a CCND1 and a MYC rearrangement.

2. Case Report

58 years old Chinese male presented with sudden onset of left sided body weakness for 2 days. It was associated with diplopia, right sided facial asymmetry and left eyelid drooping. He had loss of appetite and right neck swelling 1 week before admission. Examination revealed small right lower neck lump, mild hepatomegaly but no splenomegaly and small left lower cervical lymph node. Neurological findings noted right 7^{th} CN palsy, left 3^{rd} nerve palsy and 6^{th} CN nerve palsy, left sided upper and lower limb weakness. FBC showed leucocytosis (32,600/L× 10^9/L), anaemia (10.2g/dL) and thrombocytopenia (11x10^9/L). Peripheral blood smear interestingly showed 50% abnormal lymphoid cell (Figure 1). Serum LDH was markedly elevated at 9,271 U/L.

His admission was complicated with acute renal failure secondary to spontaneous tumor lysis syndrome with urea 22.6 mmol/L, potassium: 3.9mmol/L, creatinine: 217 umol/L;corrected calcium :2.17mmol/L; phosphate :2.74mmol/l and uric acid of 1646 Umol/L.

Both CT and MRI brain however did not show abnormality. CT neck, thorax, abdomen and pelvis showed multiple small left supraclavicular and abdominal lymphadenopathy with hepatosplenomegaly as well as splenic and right thyroid nodules with mild retrosternal extension.

Bone marrow trephine biopsy showed features of B cell lymphoma with CD20, CD79a, CD10, CD5, CCND1 positive and Negative for CD34, CD3, CD23, CD43, CD30, BCL2, BCL6 and n TDT with Ki67 about 80-90% (Figure 2).

Flow cytometry demonstrated abnormal population which was CD5 positive B-NHL (CD19,20,22,79b, HLA-DR,38,10,123 positive with kappa restriction).

FISH with an IGH/CCND1/BCL2/MYC break-apart probes confirms the presence of an IGH rearrangement was detected in conjunction with CCND1 and MYC gene. *(Figure 3)* FISH with a BCL2 break-apart probe is negative.

Patient was given R-DAEPOCH with IT- MTX. Bone marrow as-

piration and trephine biopsy done after 3 cycles showed no abnormal lymphoid population. Patient successfully completed 6 cycles of R-DAEPOCH. End of treatment PET-CT scan showed complete metabolic response with no residual lesion seen. At 18 months' post diagnosis, patient is still in complete remission (Figure 3).

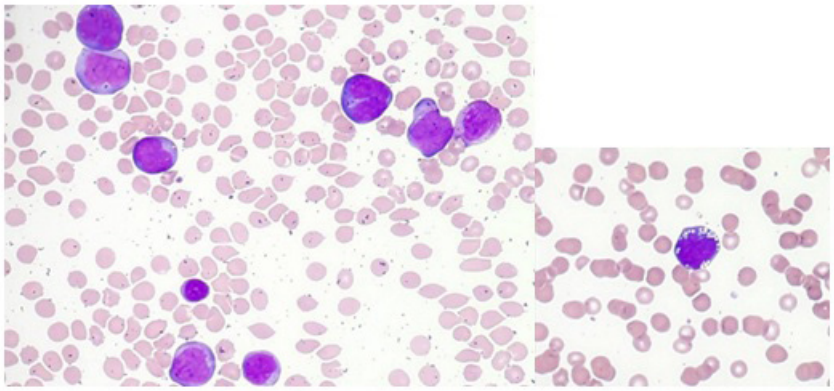

Figure 1A: Circulating large Lymphoma cell
B: Basophilic and vacuolated cytoplasm mimicking Burkitt cell.

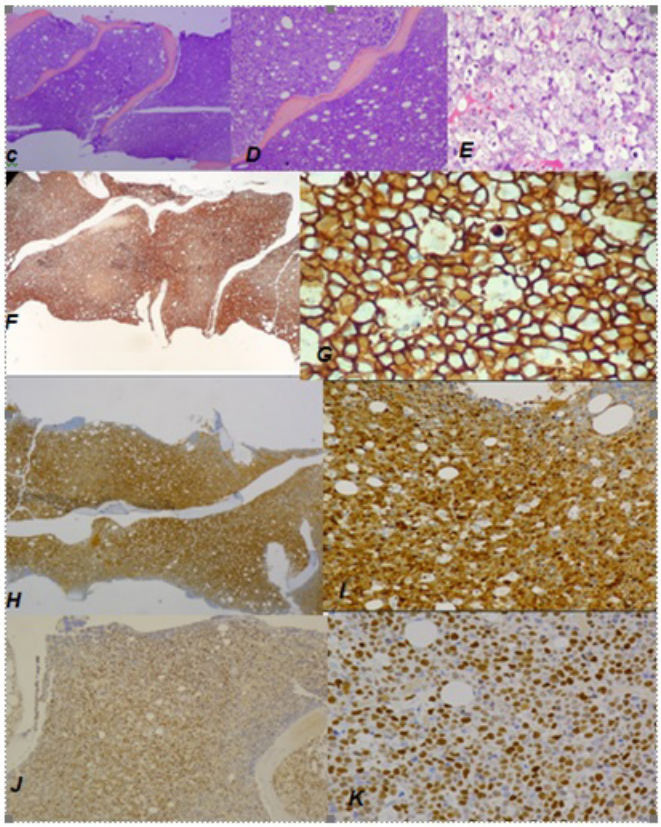

Figure 2: H & E 4x;10x C& D: Hypercellular marrow with diffuse infiltration of abnormal lymphoid cells E: The tumor cells are medium to large in size with numerous tangible-body macrophages, imparting a starry-sky appearance
F&G CD20 10x ,40x The abnormal lymphoid cells are immunoreactive to CD20 H&I cyclinD1 4x ,20xThe neoplastic cells strongly express cyclin D1
J&K C-myc 10x ,40x The abnormal lymphoid cells show nuclear positivity for C-MYC

3. Discussion

We described a case of aggressive B-cell lymphoma with both c-myc and ccnd1 rearrangement. The phenotype of the lymphoma cells was CD5+, CD10+, cyclin D1+, c-myc+, and BCL2-. CCND1+/MYC+ B-cell Lymphoma had been described in 10% of 326 Double- Hit and Triple-Hit lymphoma cases in the Mitelman database [5]. There is synergy between *CCND1* and *MYC as* cyclin D mediates G_1-S phase transition. *MYC* activation may allow the cells to be in an advantageous metabolic state to progress further. Acquisition of a *MYC* translocation is associated with a dramatic morphologic change in Mantle Cell Lymphoma (blastic or even mimicking Burkitt Lymphoma) [6] (Figure 4).

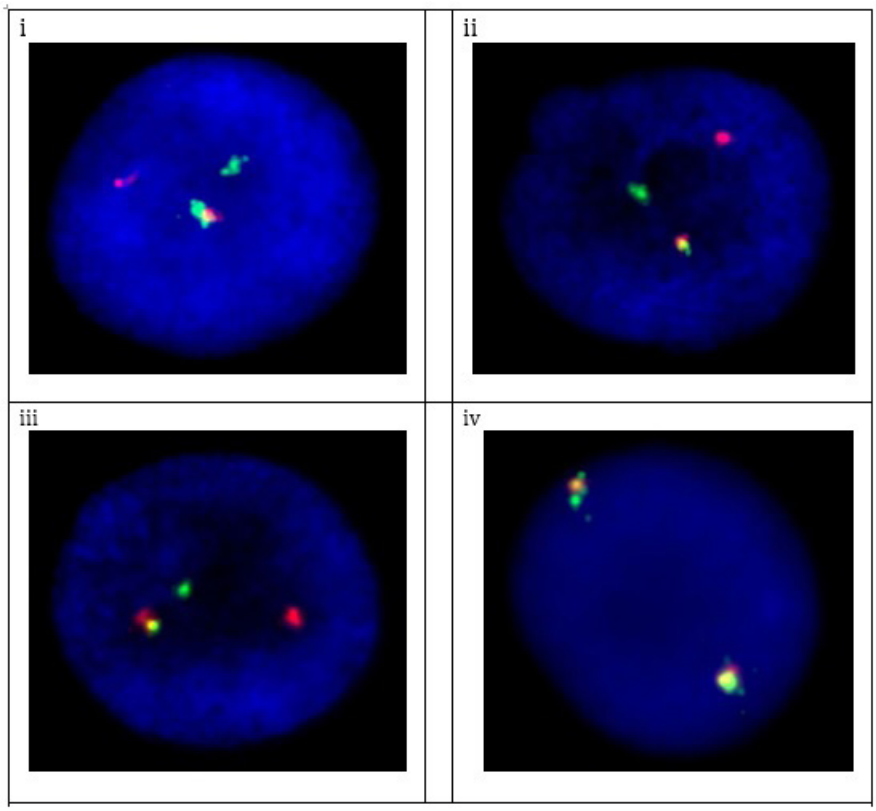

Figure 3: FISH analysis showed one fusion signal (juxtaposition of red and green), one with red and green split signals indicating gene rearrangement with IGH (14q32) [i], c-MYC(8q24) [ii] and CCND1 (11q13) [iii] break-apart probes; two fusion probes indicating normal signal with BCL2 (18q21~q22) break-apart probe [iv].

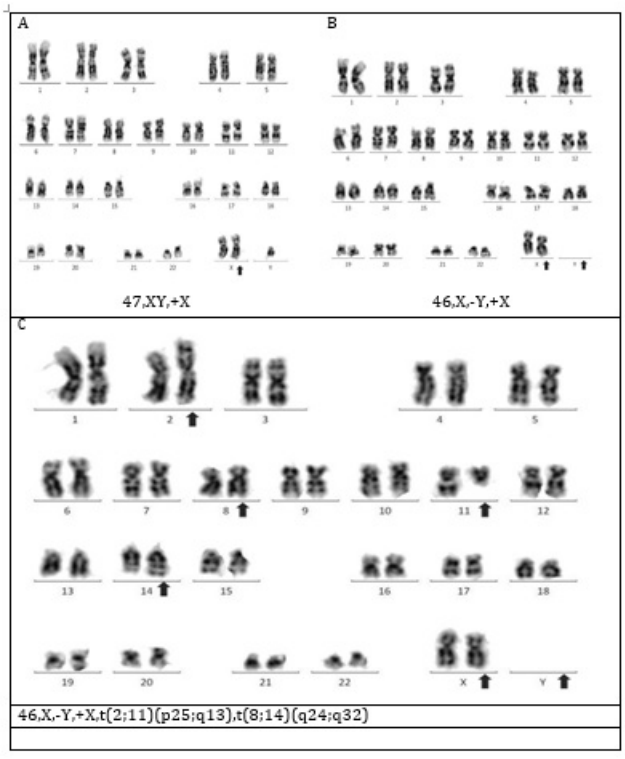

Figure 4: G-banded karyotyping (A to C) revealed 47, XY, +X [14] /46,X,-Y,+x[2] / 46, sl, t(2;11)(p25;q13),t(8;14)(q24;q32)[5] / 45,sdl1,del(5)(p13),-13[1]. Three cell lines were observed with majority had 47, XY, +X. Five of the analysed spreads showed loss of Y chromosome and gains of chromosome X, t (2;11) and t(8;14). Arrows indicates the present of abnormal chromosomes.

4. Conclusion

Our case report provides further evidence supporting the concept of "double-hit" high grade B cell lymphoma with co-involvement of MYC and CCND1 gene rearrangement which is yet to be clearly defined within (2017 revised) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. We considered that these $CCND1^{+}/MYC^{+}$ lymphomas should be separated from other lymphoma.

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