

Synchronous Diffuse Large B-Cell Lymphoma and Malignant Clonal Plasma Cells in Bone Marrow As Primary Presentation: A Diagnostic and Therapeutic Challenge

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ABSTRACT

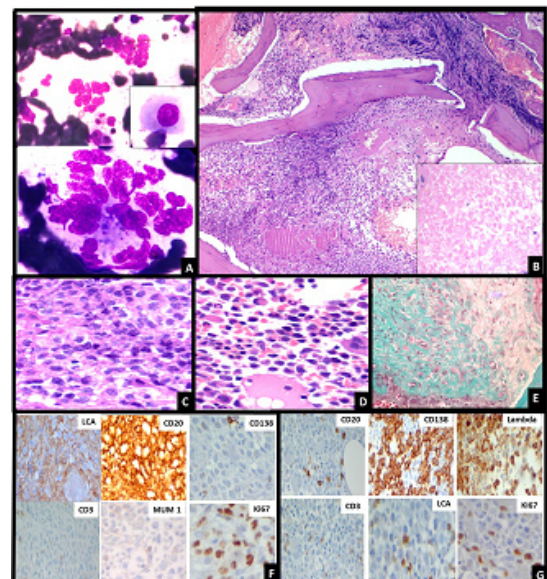
Coexistence of Diffuse Large B-Cell Lymphoma (DLBCL) with other morphologically and phenotypically distinct lymphoid neoplasm although unusual, has been reported in literature. The most common lymphoid neoplasms associated with DLBCL are Hodgkin's lymphoma, mantle cell lymphoma and marginal zone lymphoma. However, they have been reported predominantly in the sites other than the bone marrow. Rarely, DLBCL associated with paraproteinemia of IgM type, result of monoclonal plasma cell proliferation, has also been reported in literature. There is either an associated increase in the free light chain levels or disruption in the normal kappa: lambda ratio. However, co-existence of DLBCL with malignant non secretory clonal plasma cells, diagnosed primarily in the bone marrow has not been reported in the literature.

Keywords: Chemotherapy, Fibrosis, Hodgkin's lymphoma

CASE REPORT

A 72-year-old male complained of pain in left pelvis since January 2014. He had a past history of road traffic accident in September 2013; had pain left pelvis till November 2013 which then got relieved. On examination, no organomegaly or peripheral lymphadenopathy was noted. Magnetic resonance imaging (MRI) was done which showed multiple osseous lesions in pelvic bones including entire left iliac bone. Positron emission tomography (PET-CT) did in February 2014 revealed FDG avid subtle osteolytic lesions involving the pelvic bones and head of left femur. Prostate was enlarged and demonstrated heterogenous attenuation. CA 19-9, Carcino-embryonic antigen (CEA) and prostate specific antigen (PSA) levels were normal. Serum protein electrophoresis, immunofixation and free light chain assay were normal. Liver, renal function tests and lactate dehydrogenase levels were within normal limit. The peripheral blood showed leucoerythroblastic blood picture. The bone marrow aspirate and imprint smears [Table/Fig-1a-g] were hemodilute and show clusters of atypical large cells along with occasional abnormal plasma cells, suggesting an infiltrative pathology in the marrow [Table/Fig-1a]. However, the bone marrow biopsy showed cellular marrow spaces, with areas of marrow necrosis [Table/Fig-1b] (coagulative, single cell type) along with extensive fibrosis and crushing confirmed by Masson's trichrome stain [Table/Fig-1e]. There were two separate areas of distinctive histomorphological features noted. One area showed monomorphic population of large atypical round to oval cells, with scant to moderate amount of cytoplasm and prominent nucleoli, surrounded by large areas of fibrosis [Table/Fig-1c]. These large cells were positive for CD 45 (Dako, 2B11+PD7/26), CD20 (Dako, L26), CD 10 (Dako; 56C6), Bcl 6 (Dako; PG B6p) and PAX-5 (Biogenix; ZP007), but negative for CD138 (Dako, M115), CD3 (Dako, IS503), CD117 (Biogenix, YR145), MPO (Dako, IS511), MUM 1 (Dako; MUM1p), CD30 (Dako; Ber-H2), EMA (Dako; E20), ALK (Dako; ALK 1) and CK (Dako, AE1+AE3) [Table/Fig-1f]. The Ki-67 labeling index was 30%-40%. The other adjacent preserved marrow space showed mature and immature plasma cells with plasma blasts having prominent nucleoli, some showing intranuclear and

intracytoplasmic inclusions [Table/Fig-1d]. These cells were positive for CD138 with lambda restriction (Biogenix, HP 6054), MUM 1 and were negative for CD 45, CD 20, CD10 and PAX-5 [Table/Fig-1g]. Based on these two distinct malignant populations, probability of



[Table/Fig-1a]: Imprint smears showing clusters of atypical cells with predominantly bare nuclei (Leishman and Giemsa, x 400 and x1000) with scattered plasmablast (inset; x1000) **[Table/Fig-1b]:** Bone marrow biopsy showing marrow space replaced by monomorphic sheets of large cells with adjoining space showing fibrosis (Hematoxylin and Eosin, x 200). Another adjoining marrow space shows large areas of individual cell necrosis (Inset; Hematoxylin and Eosin, x 600) **[Table/Fig-1c]:** Sheets of monomorphic large cells with large irregular nuclei, some showing prominent nucleoli (Lymphoma component). (Hematoxylin and Eosin, x 1000) **[Table/Fig-1d]:** Adjacent bone marrow space shows increase in plasma cells with plasmablasts, some showing intranuclear (inset; x 1000) and intracytoplasmic inclusions. (Hematoxylin and Eosin, x 1000) **[Table/Fig-1e]:** Increased areas of fibrosis with collagen deposition (Masson's Trichrome stain, x 400) **[Table/Fig-1f]:** Immunohistochemistry markers on the lymphoma component; positive for CD45(LCA), CD20, and negative for CD138, CD3, MUM - 1 and Ki-67 index 30% - 40% (x 1000) **[Table/Fig-1g]:** Immunohistochemistry markers on the malignant plasma cell population; negative for CD45, CD20, kappa and positive for CD138 with lambda restriction and Ki-67 index 30% - 40% (x 1000)

DLBCL consistent with a neoplastic plasma cell component was kept. Due to advanced age, patient denied further workup such as molecular studies. Keeping in mind the general condition of the patient, his co-morbidities and his preference for palliative therapy, he was started on CVP chemotherapy (Cyclophosphamide, Vincristine and Prednisolone). Till date, he is responding well to treatment.

DISCUSSION

Bone marrow involvement in DLBCL at the time of diagnosis seen in approximately 10% to 25% of patients [1,2] Co-existent low grade lymphomas with DLBCL has been reported in literature [3,4]. There is also documented evidence of DLBCL with paraproteinemia due to clonal plasma cell proliferation [5]. However, demonstration of both DLBCL with malignant non-secretory plasma cells in the bone marrow in adjacent marrow spaces is unique and has not been reported in literature. The possibility of DLBCL with plasmablastic differentiation [6,7] has been excluded as the lymphoma component was CD 20/CD 45/PAX 5 /CD 10/Bcl-6 positive and lacked CD 138/MUM-1. The CD 10/Bcl-6 expression on these lymphoid cells is unique in conferring this germinal centre phenotype, a fact unknown in plasma cell lineage (they being post germinal centre terminally differentiated cells). The other population which is that of clonal plasma cells had an exact opposite phenotype with positive CD 138/MUM-1 and negative CD 45 (highly unusual for DLBCL)/CD 10/CD 20. Though some of the DLBCL cases can show CD 138 expression, they are typically positive for CD 20/CD 45 /CD 10 or MUM-1. Thus, the above findings favor this case as one with two separate coexistent malignant cell populations on bone marrow biopsy. These findings are very unusual and are the first encountered in our clinical practice.

These findings also throw certain unique diagnostic and therapeutic challenges:

1. The exact nomenclature of this lesion; whether DLBCL and myeloma or DLBCL with clonal plasma cells (non secretory type)? The absence of M spike and normal serum free light chain levels also complicate the issue. The osteolytic lesions cannot be attributed with certainty to the lymphomatous or the neoplastic plasma cell component.

2. How to treat these lesions? As primary lymphoma or myeloma therapy or a combination targeted therapy is required.
3. Prognosis of this entity should be studied further, as DLBCL with paraproteinemias as well as DLBCL with plasmablastic differentiation has a poor prognosis and is a therapeutic challenge. [4,5].
4. The putative mutations/ genetic alterations causing such a rare event.

CONCLUSION

This case highlights the diagnostic and therapeutic challenge faced in modern day oncology practice, when there is a synchronous involvement by two diverse malignant pathologies in a single biopsy specimen. Awareness of their existence and appropriate diagnostic approach would open future areas of research in learning about their biological behavior as well as exploring newer therapeutic options.

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