CASE REPORT

A Case of Lymphoma with Multiple Identities

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ABSTRACT

Discordant lymphoma (DL) is the coexistence of two or more distinct subtypes in separate anatomic sites. There are limited reports on DL cases especially involving more than two subtypes in more than two sites. We report a 76-year-old man who presented with constitutional symptoms, flank mass and painless lymphadenopathies for six months. Laboratory tests revealed moderate anaemia, markedly elevated serum IgM (13400 mg/dL), IgM Lambda paraproteinemia and Lambda light chain paraproteinuria with unmeasurable serum lactate dehydrogenase due to hyperviscous sample. CT scan showed multiple subcutaneous masses over chest wall and retroperitoneum, with lytic bone lesions, and hepatosplenomegaly. Further biopsy findings with morphological, immunohistochemical and molecular analysis of the tissue sections revealed diffuse large B-Cell lymphoma in the chest wall mass, follicular lymphoma in the inguinal lymph node and lymphoplasmacytic lymphoma in the bone marrow. This case highlights the rare DL. The importance of histopathological evaluation of lymphoma despite the availability of PET-CT scans for disease staging is undeniable.
Malaysian Journal of Medicine and Health Sciences (2023) 19(5):431-434. doi:10.47836/mjmhs19.5.50

Keywords: Discordant lymphoma, Diffuse large B-Cell lymphoma, Follicular lymphoma, Bone Marrow

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INTRODUCTION

Discordant lymphoma (DL) is the simultaneous presence of two or more histological subtypes of lymphoma in separate anatomic sites for. In contrast, concordant lymphoma (CL) is the simultaneous presence of similar lymphomas in different tissue sites (1). There is another lymphoma entity called composite lymphoma, where different subtypes of lymphoma occur within the same tissue site (2). It is reported that around 10%-15% of patients with diffuse large B-cell lymphoma (DLBCL) have concurrent indolent lymphoma at the time of diagnosis either in the same tissue or in the bone marrow (BM)1. From the previous literature review, majority of the DL is DLBCL and follicular lymphoma (FL) (2). The DL was reported to be associated with better overall survival (OS) and progression-free survival than CL (1). There are minimal reports on DL involving more than two subtypes, with Lymphoplasmacytic Lymphoma (LPL) being the least found subtype of DL. Herein, we report a case of DL comprising of extranodal DLBCL in the chest wall with follicular lymphoma (FL) in the inguinal lymph node (LN) and LPL in BM.

CASE REPORT

A 76-year-old-man presented with lethargy for six months' duration associated with right flank swelling, left axillary swelling, weight loss and loss of appetite without any fever or drenching night sweat. Clinically there were multiple painless lymphadenopathies over the bilateral cervical and inguinal region, with hepatosplenomegaly and multiple fixed swelling at the right flank.

Full blood count showed haemoglobin 8.7 g/dL, WBC 5.0x10^9/L, absolute lymphocyte counts 2.0x10^9/L, and platelet count 183x10^9/L. Peripheral blood smear revealed rouleaux formation with 1% lymphoplasmacytoid cells. The biochemical test showed hypercalcemia (corrected calcium 2.95mmol/L), raised serum creatinine of 129.1umol/L, and reversed albumin to globulin ratio with markedly elevated serum IgM (13 400mg/dL). The serum and urine electrophoresis test

revealed a predominant IgM Lambda band (65.3 g/L) and with other oligoclonal bands associated with excess Lambda light chain paraproteinuria (114.3 mg/L). Serum LDH was unattainable due to hyperviscous sample.

The diagnostic computed tomography (CT) scan (Figure 1) of the thorax, abdomen and pelvis displayed left external iliac node enlargement, largest measuring 1.1 cm; bilateral inguinal lymphadenopathy more on the left side, largest measuring 1.2 cm with no cervical lymph node (LN) swelling detected. There were multiple subcutaneous solid masses over mediastinum and left retroperitoneum with the largest lesion at left anterior chest wall measuring 3.7x6.8x6.9 cm as well as multiple lytic bone lesions with the impression of metastatic deposits from lymphoma. Further bone marrow aspiration (BMA) and trephine biopsy, chest wall mass biopsy, and left inguinal LN biopsy were done for confirmation.

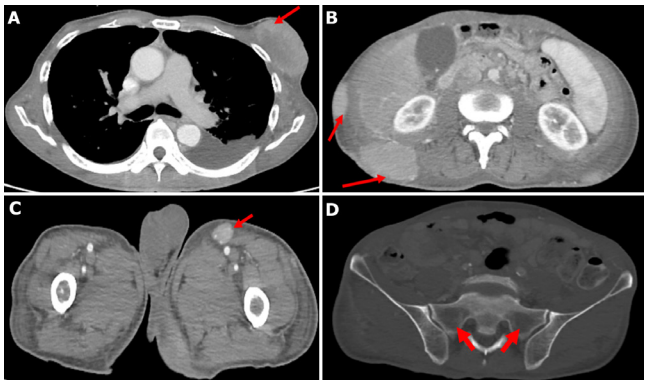

Figure 1: CT scan of thorax, abdomen and pelvis as indicated by red arrows showed subcutaneous left anterior chest wall mass with central necrosis (A), large right flank mass (B), left inguinal lymphadenopathy (C), and ill-defined lytic bone lesions at sacrum (D).

The BMA (Figure 2) showed hypercellular marrow with lymphocytosis of 30% and 5% plasma cells. There was no abnormal lymphoid in the BMA. The erythropoiesis and granulopoiesis were reduced, whereas megakaryocytes appear adequate. The trephine biopsy features (Figure 2) were compatible with low-grade B-cell lymphoma with plasmacytic differentiation in favour of LPL. There was an infiltration of the abnormal lymphoid population in a mixed pattern over paratrabecular and central areas, composed of small and monomorphic lymphocytes, lymphoplasmacytoid cells with clumped chromatin and inconspicuos inconspicuous nucleoli admixed with increased numbers of plasma cells arranged in small clusters as highlighted by CD138 stain. The lymphoproliferative infiltrates were positive for CD20 and BCL2 with low Ki67 (10% to 20%) expression but negative for CD3, CD5, CD10, BCL6, CD21, CD23 and Cyclin D1. Kappa and Lambda in situ hybridization studies showed Lambda light chain restriction.

Interestingly, the inguinal LN biopsy (Figure 3) revealed FL grade-3B. Tissue sections showed partial effacement of the LN architecture by malignant cell infiltration,

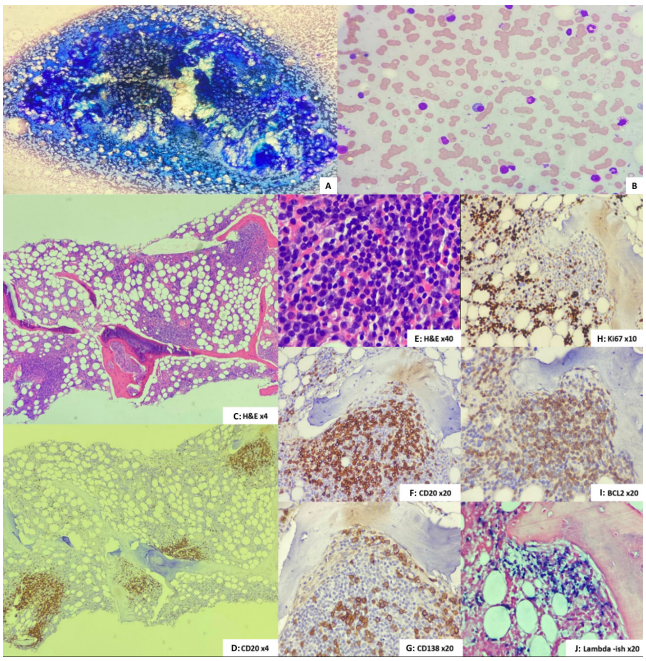

Figure 2: (A & B) Bone marrow aspirate findings showed hypercellular fragments with lymphoplasmacytoid (30%) and plasma cells(5%). Bone marrow biopsies (C, D, E, F, G) showed paratrabecular and nodular lymphoid aggregates. The infiltrate composed predominantly of small B-lymphocytes (highlighted by CD20 stain) admixed with plasma cells (highlighted by CD138 stain) and plasmacytoid lymphocytes. Ki67 (H) expression showed low proliferative activity. BCL2 (I & J) immunohistochemical staining and Lambda in situ hybridization (ish) highlight the neoplastic cells with Lambda light chain restriction.

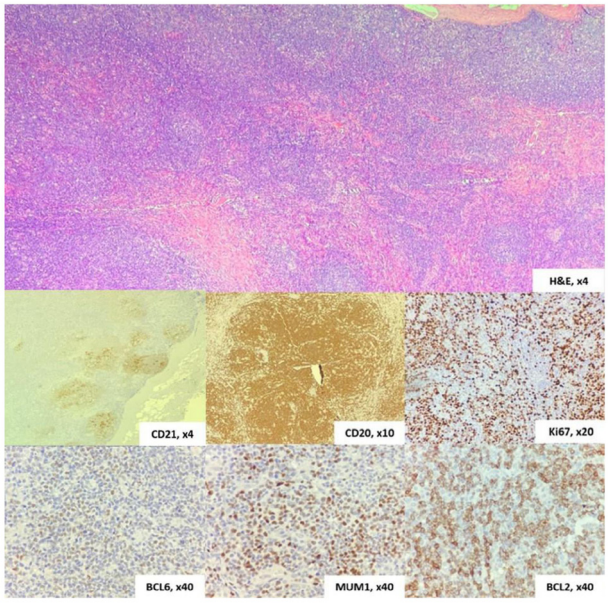

Figure 3: Follicular lymphoma, grade 3B. The inguinal lymph node biopsy showed an abnormal lymphoid nodule with residual germinal centres. Immunohistochemical studies showed the malignant cells were positive for CD20, BCL2, MUM1 and BCL6 with high expression of Ki67 (90%). The CD21 stain showed disrupted follicular dendritic cell meshwork of the residual germinal centres.

arranged in a nodular and diffuse pattern with parafollicular expansion. Occasional residual germinal centres were noted. The malignant cells were large, displaying pleomorphic, vesicular nuclei, conspicuous nucleoli and scanty cytoplasm with frequent mitotic figures and apoptotic bodies. Occasional scattered plasma cells, highlighted by CD138, were seen. Immunohistochemical studies showed positivity for CD20, BCL2, MUM1 and BCL6 with high Ki67 proliferative index expression (90%). They are were negative for CD3, CD5, CD10 and cyclin-D1. CD23 and CD21 showed disrupted follicular dendritic cells (FDC) meshwork of the residual germinal centres. Fluorescence in situ hybridization (FISH) analysis for the BCL2 gene using a break-apart probe (DAKO) showed many nuclei with normal and trisomy signals (no split signals), i.e. which indicates no evidence of BCL2 gene rearrangement.

Chest wall mass biopsy confirmed the diagnosis of DLBCL (activated B-cells subtype, ABC) according to Hans algorithm. Here, tissue (Figure 4) sections showed three strips of tissue diffusely infiltrated by malignant lymphoid cells interspersed with small lymphocytes. The malignant cells were large, displaying hyperchromatic nuclei, conspicuous nucleoli and scanty cytoplasm with frequent mitotic figures and apoptotic bodies. Immunohistochemical studies showed diffuse positivity for CD20, MUM-1, and BCL2, focally positive for BCL6, negative for CD3 and CD10, whilst CD21 was negative for FDC meshwork. The Ki-67 proliferative index was high (95%).

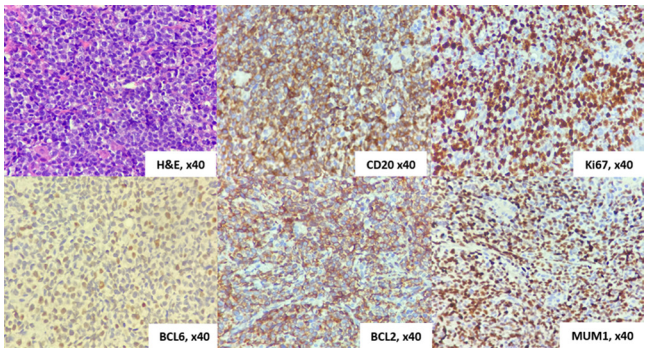

Figure 4: Chest wall biopsy exhibited diffuse malignant lymphoid cells infiltration which were large in size with hyperchromatic nuclei, conspicuous nucleoli and scanty cytoplasm. Immunohistochemical studies showed positivity for CD20, MUM-1, BCL2 and BCL6. The Ki-67 proliferative index is high (95%).

He was diagnosed with extranodal DLBCL in the chest wall, FL in the inguinal LN and LPL in the bone marrow with the revised international prognostic index for DLBCL (R-IPI) of 4, indicating a poor prognosis. In view of his age, the patient was started on Rituximab and Reduced Dose CHOP (R-mini-CHOP) for 6 cycles. Doxorubicin was omitted from the protocol due to heart failure. The disease monitoring was mainly done via PET-CT scan, and bone marrow aspiration and biopsy, whereas the paraprotein level was only performed at diagnosis. The interim PET-CT, after 2 cycles of chemotherapy, showed a good chemoresponse. However, after the complete treatment of 6 cycles of chemotherapy, a PET-CT scan revealed both FL and DLBCL had progressed in size. Salvage therapy with Rituximab-Bendamustine was then commenced. Unfortunately, after 3 cycles of chemotherapy, the PET-CT scan showed no response with new lesions at the right frontal lobe, suspicious of metastasis and an increase in the size of the axillary node.

He also developed altered mental status with disorientation, forgetfulness and became dependent for activities of daily living. Subsequent contrast enhanced computed topography (CECT) of the brain revealed secondary CNS lymphoma over the right frontal subependymal, intra parenchymal, and leptomeningeal lesions with bilateral frontal lobe leptomeningeal enhancement. In view of his advanced age and co-morbidity, more intense chemoradiotherapy
was not considered suitable. Eventually, he was referred to hospice care.

DISCUSSION

We present a rare case of DL, a condition often underreported due to symptom absence or failure in second tumor identification by clinicians (3). A study of 1324 patients explored DLBCL and concurrent indolent NHL, revealing 87.1% with DLBCL alone and 12.9% with both DLBCL and indolent NHL, primarily FL (2). DL's origin remains elusive, often discovered accidentally or linked to factors like weakened immunity, viral infections, or anti-tumor therapy (1).

Clinical manifestations in DL and de novo DLBCL or CL lack distinction, as seen in our patient (2). Treatment responses vary; concordant bone marrow involvement predicts worse outcomes (1). Our case's diagnosis and cell-of-origin classification used the Hans algorithm, revealed non-GCB subtype DLBCL (2). Chest wall biopsy showed diffuse malignant cell patterns, while inguinal lymph node histopathology favored FL (2). Unique CD10-/MUM1+ immunophenotype, absent t(14;18) translocation, and Ki67 staining pattern were noted (2).

Distinguishing histological transformation from discordance posed a challenge. FISH analysis was negative for t(14;18), yet morphology and immunohistochemistry favored FL (2). LPL transformations to DLBCL are rarer, identified by MYD88 L265P mutation (2). PET-CT and bone marrow biopsy complement each other in DLBCL staging (2). Clonality studies and immunoglobulin gene rearrangements aid DL diagnosis (2). Flow immunophenotyping enhances morphological detection of BM involvement (2).

DL treatment complexities differ from single cases (2).

Despite DL's often better survival, our patient's high R-IPI score and activated B-cell subtype indicated poor prognosis (2). Aggressive anthracycline-based chemotherapy like R-CHOP is typically used (2). Accurate diagnosis and histological classification are crucial for proper treatment and prognosis (2).

CONCLUSION

We report a rare case of DL comprising extranodal DLBCL in the chest wall, FL in the inguinal LN and LPL in BM. The constellation of history and clinical findings, biochemical investigations, imaging modalities mainly, tissue biopsy, bone marrow aspirate and trephine biopsy are mandatory to diagnose and prognosticate lymphoma. Detailed histopathology evaluation with ancillary studies mainly morphology, immunohistochemical stains and utilization of molecular tests such as fluorescence in-situ hybridization are essential to confirm the diagnosis and distinguish between true discordance or disease transformation. Additional research can determine an accurate incidence of DL and perhaps a new entity could be established for DL to avoid misdiagnosis and erroneous therapy.

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