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Case Report
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Early Post-Transplant Relapse in a Patient with Transformed Follicular Lymphoma – A Case Report

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Abstract

Histological Transformation (HT) in Follicular Lymphoma (FL) to aggressive Diffuse Large B Cell Lymphomas (DLBCL) is a major event in the natural history of indolent lymphomas and has a poor prognosis. Salvage chemotherapy followed by High Dose Therapy (HDT) and Autologous Stem Cell Transplant (ASCT) is the standard treatment. Early relapse following ASCT is rare with limited treatment options. A forty-six-year-old male was diagnosed with Stage IV Non-Hodgkins Lymphoma (NHL), Follicular Grade IIIA, Follicular Lymphoma International Prognostic Index (FLIPI) score-3 and attained metabolic Complete Response (CR) following chemotherapy and radiotherapy to residual nodal disease. Six years later he had disease relapse with HT to DLBCL, Double Expressor (DE) stage IIIA. He underwent salvage chemotherapy and consolidation with ASCT. Three months later he developed thrombocytopenia and non-oliguric renal dysfunction. PET-CT (Positron Emission Tomography) showed multiple hypoattenuating lesions in the liver, left kidney, intraabdominal lymphadenopathy and skeletal lesions. Renal biopsy revealed High grade B cell lymphoma – DE and was diagnosed with early post-transplant relapse in transformed FL. Shortly he developed sepsis with multiorgan dysfunction syndrome and succumbed to the disease. The case is being presented in view of its rarity.

Keywords: Histological transformation; Double expressor lymphoma; Post-transplant relapse; Transformed follicular lymphoma; Autologous stem cell transplant

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Introduction

Follicular Lymphoma (FL), the commonest indolent non-Hodgkin's lymphoma (NHL) transforms to aggressive subtypes (3% per year) commonly Diffuse Large B Cell Lymphoma (DLBCL) [1]. Histological Transformation (HT) to Double Expressor/Double Hit Lymphomas (DEL/DHL is rare and has a poor prognosis with a median survival of 10 to 12 months [1,2]. Salvage chemotherapy followed by Autologous Stem Cell Transplant (ASCT) is the standard treatment [3]. The 5-year Overall Survival (OS) and Progression Free Survival (PFS) of transformed lymphoma treated with ASCT is 60% to 70% and 40% to 45% respectively. Cause of death due to disease progression is seen in 60% of the patients treated with ASCT [4]. We report a rare case of HT of FL to DEL and early relapse after ASCT.

Case Presentation

A 46-year-old male diagnosed with Stage IV NHL, FL Grade IIIA, Follicular Lymphoma International Prognostic Index (FLIPI) score-3, received two cycles of Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone (R-CHOP) and four cycles of CHOP (rituximab omitted due to hypersensitivity) followed by radiotherapy to the residual paraaortic nodal mass. He attained Complete Metabolic Response (CMR) and six years later disease relapsed with bulky paraaortic, mesenteric, pelvic nodes, and mass in left parapharyngeal region and nasopharynx. Biopsy was suggestive of NHL-DLBCL, Double Expressor (DE) stage IIIA, International Prognostic Index (IPI) score-2. He attained a second CMR following three cycles of salvage chemotherapy (ICE regime) and was consolidated with ASCT (Granulocyte Colony Stimulating Factor (GCSF) mobilization and (BCNU, etoposide, cytarabine and melphalan) BEAM as conditioning regime).

Three months later, he developed thrombocytopenia and non-oliguric renal dysfunction. Clinical examination was unremarkable. Ultrasound abdomen showed no evidence of obstructive uropathy. Nephrology opinion was sought and was started on methyl prednisolone. Thrombocytopenia improved on steroids. Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-d-

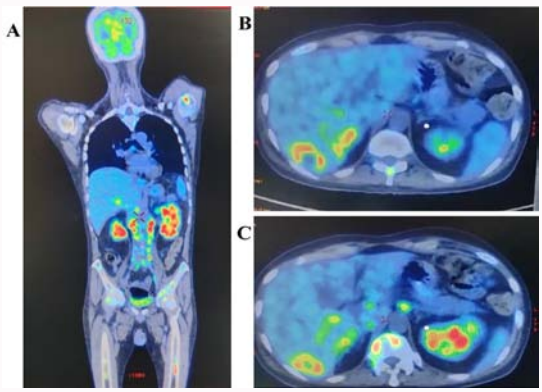

Figure 1: A) PET-CT showing bilateral renal metastasis, liver lesions, intraabdominal lymphadenopathy and skeletal metastasis. B) Axial PET-CT image showing liver metastasis. C) Axial PET-CT image showing left renal enlargement, renal and liver metastasis.

glucose integrated with Computerized Tomographic (PET/CT) scan showed multiple hypoattenuating lesions in the liver, both kidneys, intraabdominal lymphadenopathy and skeletal lesions (Figure 1). Bone marrow biopsy revealed hypoplastic marrow. Renal biopsy showed infiltration by High grade B cell lymphoma – DE (CD20 +ve, CD5 -ve, bcl2 +ve, bcl6 +ve, C myc positive with MIB-1 - 60%) (Figure 2). He was diagnosed with early post-transplant relapse in transformed FL. A week later he developed progressive cough and dyspnea. Computed tomographic scan of thorax was suggestive of fungal pneumonia. Subsequently, he developed sepsis with multiorgan dysfunction syndrome and succumbed to the disease.

Discussion

Follicular Lymphoma commonly progresses to higher grades of lymphoma, years after diagnosis through acquisition of recurrent genomic driver mutations at the rate of 2% to 3% per year [1,5]. Clinical transformation is suspected when patients with indolent lymphoma develop rapid localized nodal growth, new B symptoms or rapidly rising serum Lactate Dehydrogenase (LDH) level [5]. Diagnostic biopsy shows large cells diffusely infiltrating lymph nodes leading to effacement of the follicular architecture [3]. Montoto et al. reports transformation rate of 17% and 28% at 5 and 10 years respectively [6]. Grade 3 histology, high FLIPI score, advanced age, low serum albumin, high serum LDH, B symptoms, MYC and BCL6 translocation at diagnosis are associated with high risk of HT [5,7,8]. Diffuse large B cell lymphoma is the commonest subtype. Rarely double or triple hit lymphomas are seen [1]. The majority of transformed FL retain the phenotype of the underlying FL (expression of CD10, BCL6 and BCL2 is retained). The Gene Expression Profiling (GEP) of HT is that of Germinal Centre Subtype (GCB) [9]. Changes in expression of MYC and its target genes to confer high risk [10].

No prospective data exist to guide therapy for transformed FL. Treatment approach depends on whether or not a patient is treatment naïve, type of treatment received for prior indolent lymphoma and the histology at transformation [11]. Patients with Double Expressor Lymphoma (DEL) and Double Hit Lymphoma (DHL) may be treated with more aggressive strategies such as DA EPOCH (Dose Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin). Patients who received prior anthracycline-based therapy should be considered for salvage therapy and consolidation with ASCT [11]. Our patient was treated with RCHOP at initial

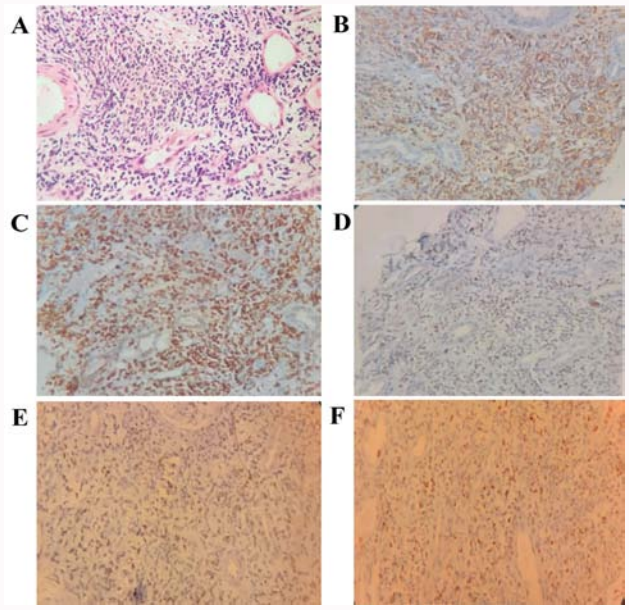

Figure 2: A) Linear core of renal parenchyma with diffuse interstitial infiltrate of atypical lymphoid cells - Hematoxylin and Eosin (H&E 400×). B) Immunohistochemistry (IHC) showing CD20. C) IHC showing BCL2. D) IHC showing BCL6. E) IHC showing Cmyc. F) IHC showing Ki 67.

diagnosis and developed HT to an aggressive DEL. He received salvage chemotherapy with ICE regime followed by consolidation ASCT.

Post ASCT relapse is a major cause of treatment failure. Reddy et al. studied a cohort of 57 patients with transformed NHL with a median follow up of 3 years after Stem Cell Transplant (SCT). They reported a two-year relapse rate of 37.4%. Patients receiving more than 3 chemotherapy regimens before SCT and late HT similar to this case had a trend towards increased risk of relapse [12].

Relapse at a median of 6 months post-allogeneic SCT was reported by Doocey et al. in 4 of the 16 patients with transformed B cell lymphoma, most relapses occurring within 26 months. Among the relapsed patients, 2 had aggressive histology similar to our patient. All 4 patients with relapse expired which was the outcome of this case as well [13]. On the contrary, early relapse at 3 months post ASCT was seen in our patient which is a rare phenomenon. Similarly, Villa et al. reviewed the outcome of 105 patients with HT and among the 50 patients who underwent ASCT, only 4% had early mortality (within 100 days) due to disease progression further emphasizing the fact that early relapse is rare [14]. The pattern of relapse after ASCT in this patient involving multiple extranodal sites (liver, kidney and bone) is also noteworthy.

Stage, LDH level, presence of B symptoms and response to salvage therapy were the prognostic factors for survival after HT as reported by Bastian et al. [15]. Our patient had stage III disease and raised LDH levels at HT which may have contributed to the poor outcome.

Conclusion

Histological transformation is a major cause of mortality in patients with FL. Due to its rarity, there are no randomized studies to guide management of HT. Autologous stem cell transplant may improve the outcome of chemosensitive relapses. Early post-transplant relapse is rare and difficult to manage with limited

treatment options.

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