Diffuse Large B cell lymphoma with symptoms of renal failure at initial presentation

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Abstract: We here report a case of Diffuse Large B cell lymphoma (DLBCL) with symptoms of renal failure at initial presentation. Patient was diagnosed following renal biopsy and treatment included several cycles of R-CHOP regimen. Patient initially responded well to treatment and renal function normalized over the course of treatment but relapsed soon after with CNS involvement. We conclude from our experience that treatment of DLBCL presenting with renal failure is complicated by aggressive nature of the disease, extra nodal organ involvement and likely subclinical metastasis at presentation.

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1. Introduction

Lymphomas that arise from sites other than the lymph nodes and other lymphatic organs such as the spleen, waldeyers ring and thymus are defined as extranodal lymphomas. It is seen in roughly 40% of the cases diagnosed with non Hodgkin's lymphoma (Møller MB et al., 2004).Most of the cases involve the GI tract and involvement of the kidneys accounts for a mere 1% of the total primary extra nodal lymphomas(Krol AD et al.,2003).

Patients with renal involvement in NHL don't normally have any features of flank pain or volume overload and diagnosis is done following biopsy. Its involvement however is associated with a very poor prognosis as Renal involvement is characterized by significant risk for CNS involvement(Brouland JP et al.,1994).Ongoing studies recommend clinical trials for treatment of such high risk patients and mostly debate between the use of R-HDT followed by Autologous Stem Cell Transplantation (ASCT) as a treatment strategy or R-conventional regimens followed by ASCT. Furthermore CNS prophylaxis is another debatable issue in the rituximab era as some studies have doubted the usefulness of CNS prophylaxis (Hyder AO et al., 2007) in patients that respond well to rituximab included chemo regimens owing to its enhanced ability for systemic disease clearance. Our patient however while responding well to standard R-CHOP therapy relapsed within a short span of time with CNS involvement a scenario which we believe could have been delayed with intrathecal prophylaxis.

We here report a case of extra nodal lymphoma which presented with signs and symptoms of renal failure on initial presentation which improved radically when treated with rituximab but relapsed within a short span of time with CNS involvement. We further conclude improvement of renal failure shouldn't be the goal of treatment in patients with renal involvement in Non-Hodgkin's Lymphoma (NHL) as there could be associated metastasis in other organs such as the GI tract, mediastinum, heart and the CNS.

2. Case report

A 48 year old female with no significant past medical history was admitted in our nephrology ward on Feb 15/2012 with chief complaints of chest tightness, palpitations, anorexia and vomiting. Physical examination revealed an ill looking, pale patient with a blood pressure of 160/100 mmHg. Posterior group of lymph nodes were palpable, freely moving and nontender. Systemic examination revealed no significant findings and pertinent laboratory data were as follows Hb 89g/dL, BUN, 30.81mmol / L, and Cr 678μmol / L, LDH-555.7IU/L, UA 722μmol/L. Urine R/E- Protein++0.74g/24hours, RBC 2.4/HP and WBC 8.5/HP. Immunofixation electrophoresis was negative for blood λ and κ light chains and urine λ /κ values were within normal limits. Abdominal ultrasound showed a blilaterally enlarged kidneys measuring 136×65 mm (left) and 135×70 mm(right) with normal appearing collecting ducts, ureter and bladder. No hepatosplenomegaly or free fluid were noted in the abdomen. Echo revealed a minor pericardial effusion and an ejection fraction of 53%. CT scan of the kidneys reported enlarged kidneys with irregular border. Borders between the cortex and medulla couldn't be delineated (Figure 1a).

Patient was suspected of Renal cell carcinoma and biopsy was performed. Patient was admitted with strict I/O charting, and haemodialysis 3 times a week. Urine output at this time was only 0.2L/24 hours. Kidney biopsy reported renal cortical

and medullary tissue at the borders of the mass, normal glomerular and tubular cells and large lymphocytic infiltration in the interstitium(Figure 1b). Immunohistiochemistry and special staining of the mass was highly suggestive of DLBCL as the tissue was CD20+ (Figure 1c) cytokeratinin + for residual tubules whereas Immunoglobulin λ / κ light chains, C4d, HBsAg, HBcAg,Congo red stains were all negative. Additionally Non Specific Esterase stain, Chromogranin A and CD56 stains were also negative,MPO and CD3 were weakly positive(Fig1d). Patient was transferred to our ward (Hematology/Oncology) and bone marrow smear/biopsy was done which was negative for any neoplastic infiltration. Lumbar puncture performed at that time was negative for any malignant cells.PET/CT scan done for staging of the lymphoma reported mediastinal lymph nodes with increased FDG uptake, pericardial thickening, multiple nodules involvement on bilateral breast most prominent over the lateral area of the right breast (Figure 1e), Kidneys were diffusely enlarged and uneven in density. Cortex and medulla were clearly delineated with multiple nodules visible at the level of descending aorta. Patient also had increased SUV uptake in lower segment of uterus, frontal sinus and 6th rib.

Patient was thus diagnosed with Stage IVa DLBCL with 1) Chronic renal insufficiency 2) pericarditis. Hemodialysis 3 times a weekly was continued and Chemotherapy was started. Patient was started on R-COP regimen on March 5/2012（R 500mg d0，VDS 4mg d1，CTX 0.4g d1,3,5，DXM 15mg d1-5 ， within two days of start of chemotherapy patient's urine output increased from 0.2L/day to 1L/day and normalized over the course of treatment with corresponding decrease in serum creatinine. Patient further underwent 3 cycles of R-CHOP regimen and patient responsed well to each cycle. A repeat PET/CT scan done after the chemotherapy reported a marked decrease in FDG uptake compared to earlier scans (Figure 1f). But on May 15 a couple of days following the PET/CT scan, patient's state of health deteriorated with abnormal behavior and decreased cognition. Patient was suspected of having brain metastasis and MRI /MRS was advised. The report was suggestive of intracranial metastasis involving bilateral corpus callosum and right upper part of the skull (Figure 1g), patient was referred to a specialized centre for radiation therapy where she underwent three cycles of radiotherapy and intrathecal chemotherapy consisting of MTX (10mg), DXM (5mg) and Ara-C (50mg). Patient is currently being planned for autologous stem cell transplantation following immunotherapy with CIK cells. Patient's present state of health remains stable but prognosis remains poor.

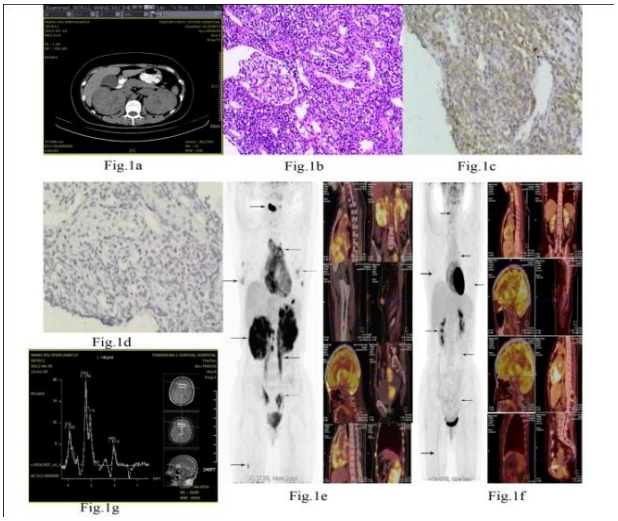

Figure 1a Abdominal CT scan showing bilaterally increased kidneys.Figure 1b Renal biopsy 10x Lymph node biopsy from the patient on diagnosis. Figure 1b Hematooxylin and eosin (H&E stain, 10X magnifications shows massive lymphocytic infiltration of the renal interstitium. Figure 1c Immunohistochemical staining positive for Anti-CD20 antibody and deposits seen in the renal biopsy. Figure 1d Immunohistiochemical staining of Anti-CD3 antibody of biopsy shows no significant deposits in the specimen. Figure1e. Legend: PET/CT scan of the patient done before treatment with hyper metabolic regions in the thyroid gland, medullary shaft of femur, right mammary glands, frontal bone, renal parenchyma, pericardium and 6th rib. The report was suggestive of diffused lymphoma; disseminated lymphoma with secondary renal involvement couldn't be ruled out as central lymphoid organs eg. The marrow of ribs, skull and femur were also involved. Figure 1g Follow up scan done after 3rd cycle of chemotherapy shows gross decrease in FDG uptake suggesting excellent response to chemotherapy. Figure 1f MRS scan of the head showing different peaks of the metastasis located at the corpus callosum and lateral ventricle. Variation is observed in the Cho and NAA peaks; change in their ratio was suggestive of malignancy.

4. Discussions

Our patient was unique as she had renal failure on intial presentation, a renal biopsy that was diagnostic of DLBCL and degrading renal function which improved rapidly upoun initiation of chemotherapy. These features suffice for a rare and

doubtful diagnosis of Primary Renal cell Lymphoma but PET/CT scan which showed dense FDG uptake in the Kidneys also revealed multiple lymph nodes involvement and like most other similar cases (Ozaltin F et al., 2004, Domazetovski I et al., 2012) diagnosis of lymphomatous infiltration of the kidney from a nodal lymphoma or other extranodal site couldn't be ruled out.

Primary renal lymphoma is a rare occurrence, most renal lymphomas are secondary to a nodal source and antedecent diagnosis of primary renal lymphoma is always difficult to make. Primary Renal lymphomas are impausible if we consider the fact that our kidneys are devoid of any lymphatics but Renal lymphomas can occur in conditions when lymphocytes are attracted to the kidneys due to infection or inflammation during the course of which an oncogenic stimuli initiates a lymphomatous process (Brouland JP et al., 1994). Similarly lymphocytes can invade the renal parenchyma from the renal capsule which unlike the parenchyma is rich in lymphatics (AO et al., 2007).

Secondary renal involvement in NHL appears to be frequent as renal involvement in systemic lymphomas is reported to be 50% in advanced cases. Aggressive B-NHL lymphomas such as Burkitts lymphoma have a large propensity towards extranodal sites and involvement of Kidneys in Burkitts lymphoma is quite common. DLBCLs and Burkitt lymphoma have characteristic morphological, immunohistochemical and cytogenetic features but burkitt like lymphoma and atypical burkitts compromise a large gray zone between DLBCL and Burkitts consequently a clear line differentiating atypical BL from DLBCL is still under speculation. Differentiating Burkitt lymphoma from DLBCL is important since treatment regimens between the two forms of lymphoma differ as Burkitt lymphomas require a high intensity chemotherapy regimen with CNS prophylaxis; however CNS prophylaxis or HDCT with stem cell support in DLBCL has no proven benefit in overall survival or Event free survival. But DLBCLs with unusual extra nodal site of involvement such as the kidneys could be considered for BL like treatment with standard chemotherapy and CNS prophylaxis. A thorough immunohistochemical analysis of our patient with BCl-2 expression and cytogenetic analysis of myc rearrangement could have been helpful in distinguishing the exact nature of the disease. This could have had complemented the rapid improvement shown by our patient under R-COP chemotherapy with prolonged remission.

The prognosis of DLBCL patients presenting with renal failure is bad whether it is an actual primary renal cell lymphoma or not. Although no actual figures exist due to the rarity of the condition, patient generally improve rapidly upuon initiation of chemotherapy, relapse earlier than most lymphomas and deteriorate then on. It can be reasoned that DLBCL patients presenting with renal failure might have subclinical widespread metastasis at initial presentation and involvement of the CNS which can be seen in as much as 36% of these patients might have a negative effect on patient survival (Villa D et al., 2011). In our case the retroperitoneal and extranodal outlook of the organs involved also couldn't be avoided. The uterus, kidneys were extensively involved with associated symptoms but the GI tract and spleen generally remained uninvolved. Both these factors were identified as independent risk factors of CNS involvement in High grade NHL (Hollender A et al., 2002) furthermore with an IPI score of 4, patient had a very poor progression free survival.

Treatment strategy for this patient was complicated as in one hand we had a very aggressive lymphoma and on the other renal failure, which was preventing the use of high dose chemotherapy. We opted for a standard dose R-CHOP regimen followed by autologous stem cell transplantation. From our experience, we could deduce Rituximab could induce remission and was a safe drug of choice in lymphoma patients presenting with renal failure. Safety and efficacy of rituximab while treating patients in hemodialysis have had good results(Feldmann G et al.,2007) and similar to our experience, studies which have used rituximab in cases of lymphoma with renal involvement have concluded it is a safe and efficient drug to use in such cases(Tokar M et al.,).But patient relapsed within 90 days of initiation of treatment which was less than desirable compared to other form of disseminated lymphomas thus it might be necessary to contemplate other treatment strategies. Recently clinical trials compared the efficacy of standard CHOP regimen and high dose CHOP like regimen with autologous stem cell transplantation rescue in improving survival of highly aggressive lymphomas. They concluded that although there was no difference in overall survival of patients in the two groups, the latter had a significantly high event free survival (Milpied N et al.,2004). Another study that compared intensive conventional chemotherapy (ACVBP regimen) with CNS prophylaxis to standard CHOP regimen concluded Intensive chemotherapy despite its higher toxicities could improve survival and EFS in patients with aggressive lymphomas. (Tilly H et al.,2003)

Although we can only speculate an aggressive regimen might have led to a different course of disease in our patient, associated renal failure and a rapid response to standard regimens

made more aggressive regimens difficult and risky choices.

It is in light to these observation and experience that patients that present with renal failure in DLBCL present a major diagnostic and therapeutic challenge, the disease can relapse within a short span of time with life threatening consequences and its treatment is complicated by aggressive nature, extra nodal organ involvement and subclinical metastasis at initial presentation.

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