

# Atypical Presentation of Transformed Follicular Lymphoma

Dingani Nkosi\* and Marie Amanze

Visiting Scholar, Florida State University, College of Medicine, Biomedical dept, Tallahassee, FL, USA

## Abstract

Transformation of follicular lymphoma (FL) to Diffuse Large B-Cell Lymphoma (DLBCL) occurs commonly and is associated with a rapidly progressive clinical course that is refractory to treatment and a short survival. The clinical presentation of this transformed disease is variable. We here report a 65 years old man with an atypical presentation of transformed FL. He initially presented with symptoms and clinical signs consistent with Multiple myeloma. His bone marrow biopsy result revealed plasma cell infiltration (CD 138+, CD56-) throughout the marrow. He had a rapid progressive worsening of his condition; he developed liver and renal failure. His imaging studies revealed diffuse lymphadenopathy, an excisional lymph node biopsy done showed FL which had transformed into DLBCL with prominent plasma cell differentiation. He was treated with of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) with overall good response but has currently relapsed.

**Keywords:** Lymphoma; Transformation; Follicular

## Background

Diffuse large B-cell lymphoma (31%) and follicular lymphoma (22%) represent the common non Hodgkin lymphoma subtypes in the western world [1]. Follicular lymphoma (FL) is an indolent incurable malignancy with a median survival of 8–10 years [2]. Transformation of FL to DLBCL does occur frequently and has been associated with a rapidly progressive clinical course that is refractory to treatment and a short survival [3]. The clinical presentation of the transformed disease is variable with most patients presenting with an advanced extent of disease. There no reported prospective studies evaluating treatment approaches in patients with transformed FL.

We here report a 65 years old man with an atypical presentation of DLBCL. He initially presented with symptoms and signs consistent with Multiple myeloma, this was complemented with hypercalcemia, anemia, elevated Beta 2 microglobulin and a plasma cell infiltration (CD138+, CD56-) on his bone marrow biopsy. His condition progressively worsened, he developed renal and liver failure while awaiting his excisional lymph node biopsy results. This was further complicated by his mental status deterioration and development of cardiac arrhythmias. The lymph node biopsy results showed FL (CD10+, BCL2+, BCL6+) which had transformed to DLBCL (CD20+) with plasma cell differentiation. He was treated with R-CHOP and had overall good response but has currently a relapse.

## Case Presentation

A 65 year old black male, a referral from Immunology and allergy Clinic presented to our hematology clinic for further evaluation of severe anemia and elevated total protein. His initial complaints were progressive body weakness and easy fatigability which was associated with dyspnea on exertion for almost a month. The patient was reported to be spending more time sleeping than usual by his wife. He also complained of intermittent pains in the right hip, knee and back. A systematic review of the patient was normal. His past medical and social history were unremarkable.

On physical examination, he had a pale conjunctiva, tachypneic and systematic examination was normal. The complete blood count done at initial consultation showed a leukocytosis of  $18.3 \times 10^9/L$  and a microcytic anemia (HB 6.2 g/dl, MCV 60.9 fl) which required transfusion. His metabolic panel showed elevated liver transaminases (AST 135 U/L, ALT 85 U/L, and LDH 446 U/L), total protein (95 g/L), hypoalbuminemia (17.1 g/L) and normal creatinine renal clearance

of 79.71 ml/ml. A bone marrow biopsy was performed and serum protein electrophoresis, quantitative immunoglobulin G samples were sent for analysis. A presumptive diagnosis of multiple myeloma was made and the patient was empirically started on Dexamethasone and Esomeprazole

His bone marrow biopsy result revealed impressive plasma cell infiltrate prominent throughout the marrow. It was CD 138 positive (4+ positive in 50% of marrow cells) and CD 56 negative. The serum protein electrophoresis showed a monoclonal M spike, his serum Beta-2-microglobulin was 3.8 mcg/mL and had hypercalcemia. A non-contrast Computed Tomographic (CT) examination of his chest, abdomen and pelvis showed no definite lytic lesions of the bones in the spine but revealed diffuse axillary, sub pectoral, and mesenteric lymphadenopathy. An ultrasound guided lymph node core biopsy was done but had insufficient tissue to make a diagnosis so he was scheduled for an excision biopsy. The patient was then commenced on Bortezomib and Dexamethasone to treat his multiple myeloma.

A week after starting the chemotherapy, he presented to the Emergency room disoriented, confused, had oral thrush and a fever of 39.4°C. Auscultation of his lungs revealed bilateral coarse breath sounds with some basilar crackles. His complete blood count still showed an elevated white cell count of  $22.5 \times 10^9/L$  which was predominantly lymphocytes. The microcytic anemia had slightly improved to hemoglobin of 7.2 g/dl and mean corpuscular volume of 70 fl. His metabolic panel results showed elevated Creatinine (2.2 mg/dl), elevated total bilirubin (3.2 mg/dl), hyperkalemia (5.2 mEq/L) and hyponatremia of 125 mEq/L. A chest x-ray done revealed bilateral pulmonary infiltrates consistent with pneumonia. The patient was treated as having Delirium due to pneumonia and was started on Vancomycin and Cefipime. He was also started on Fluconazole and Nystatin because of the oral candidiasis and Heparin for deep venous thrombosis prophylaxis. His condition had improved markedly after commencement of the treatment was discharged after 5 days of admission.

\*Corresponding author: Dingani Nkosi, Florida State University College of Medicine, Tallahassee, FL, USA, Tel: 2022817096; E-mail: [dingani.nkosi@med.fsu.edu](mailto:dingani.nkosi@med.fsu.edu)

Received April 06, 2015; Accepted May 23, 2015; Published May 26, 2015

Citation: Nkosi D, Amanze M (2015) Atypical Presentation of Transformed Follicular Lymphoma. J Clin Case Rep 5: 531. doi:10.4172/2165-7920.1000531

Copyright: © 2015 Nkosi D, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

On his follow up in clinic, he presented with jaundice and worsening lower extremity edema. His liver function tests showed elevated total bilirubin (11.9 mg/dl), direct bilirubin of 9.1 mg/dl, alkaline phosphatase of 175 IU/L, SGOT of 148 IU/L, SGPT of 38 IU/L and was still hypoalbumemic. He had also had developed acute renal failure, his creatinine was 4.5 mg/dl, blood Urea Nitrogen of 87 mg/dL, was hyperkalemic 6.32 mEq/L and hyponatremic of 134 mEq/L. The patient was treated with aggressive intravenous fluids and Kayexalate. A few days into his admission, the patient developed acute Atrial Fibrillation (AF). The patient underwent direct current cardioversion and was in sinus rhythm for about three days then reverted to atrial fibrillation. His AF was refractory to Diltiazem and beta blockers until he was switched to Amiodarone. During this admission, the patient also became delirious; he had episodes of global confusion with periods of tremor with intermittent lucency. Magnetic resonance imaging of the head showed no acute intracranial abnormality and his lumbar puncture, urine & blood cultures were negative. A neurology consult was obtained and he was diagnosed with multifactorial delirium with no specific cause. The patient was empirically treated with Vancomycin and Piperacillin/Tazobactam and all viral and bacterial cultures remained negative.

An excisional lymph node biopsy was done which revealed a diffuse large B cell lymphoma (CD20+, CD10+, BCL2+, BCL6+) with prominent plasma cell differentiation. He had stage IV disease with a poor prognosis according to the Revised International Prognostic Index with predicted 4-year progression-free survival of 53% and overall survival of 55%. The patient's condition remained relatively stable though his liver function tests results still remained elevated and the renal insufficiency was not improving. He remained confused despite a normal neurological workup. Given the diagnosis of DLBCL, he was started on modified doses of CHOP-R (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone and Rituximab) plus Neupogen. He developed mild leukopenia after his first cycle of chemotherapy. His Bilirubin and creatinine levels began slowly decreasing after the first cycle of chemotherapy. The patient was discharged to Select hospital to continue his medical care and aggressive physical therapy because he was debilitated. He received total of 6 cycles of CHOP-R and a second opinion of was obtained at Shands pathology department which indicated that the biopsies showed a follicular lymphoma and had transformed into large cell lymphoma that had morphologic and phenotypic evidence of plasma cell differentiation. This was supported by the presence of CD20+, BCL2+, BCL6+ in the initial node in keeping with follicular lymphoma, follicular cells showed a high proliferative fraction of Ki-67, a subpopulation of CD10+ B cells with phenotype compatible for follicular lymphoma, and FISH studies demonstrating both BCL2 & BCL6 (seen in transformation) gene rearrangements and negative for MALT1. Kappa and Lambda in situ hybridization showed marked lambda light chain restriction with few Kappa positive cells. Based on the morphology, high proliferative fraction and architecture of the lymph nodes, it was regarded as DLBCL.

## Discussion

Follicular lymphoma patients can have long survival times, but disease progression typically occurs 3-5 years after initial treatment. Overall, studies conducted suggest a cumulative rate of transformation FL to DLBCL of about 3% per year [4]. The transformed disease is usually incurable and has shorter disease free survival. Our patient did not have a prior diagnosis of Follicular lymphoma and was not being followed up to ascertain the duration of the disease and when the transformation occurred. This means we cannot really ascertain the risk

factors which our patient had to transform to DLBCL. Though no prior treatment has been speculated as a risk factor, Al-Tourah et al reported no difference in the risk of transformation in patients who were initially treated with chemotherapy (n=407), radiation therapy (n=90), or were on a watchful waiting strategy (n=103; P=3) [5]. The increase in the probability of transformation over time and its occurrence in both treated and un-treated FL patients suggest that the change to a more aggressive histology associated with a more aggressive clinical behavior represent an inherent potential of FL [4].

The clinical presentation of the transformed disease is variable. Most patients at the time of transformation present with an advanced extent of their disease (stage III/IV or bulky stage I/II disease with new B symptoms); however, transformation may also be diagnosed in patients with limited disease [6]. Our patient initial symptoms and clinical picture at presentation best fitted multiple myeloma which was confirmed by presence of plasma cells on the bone marrow biopsy. The presence of diffuse lymphadenopathy rather than lytic lesions on the CT scan prompted further histological examination of the nodes which revealed the diagnosis of DLBCL with plasma cell differentiation. Our patient had stage IV disease with a poor prognosis according to the Revised International Prognostic. This atypical presentation of transformed disease especially in a patient who did not have a prior diagnosis of the indolent disease necessitates a high level of clinical suspicion and work up.

There no reported prospective studies evaluating treatment approaches in patients with transformed FL. Most patients with transformed FL are treated with standard doxorubicin-containing combination chemotherapy regimens, which are reported to lead to complete remission in 40% and overall response in 60% and of patients [4,7]. Radiation, either alone or in combination with chemotherapy, is used in patients with limited disease or may lead to a higher CR rate (70%) [4]. Our patient was treated with Rituximab-CHOP since he was anthracycline naïve. After initiation of the chemotherapy, the liver and renal failure started improving and the patient finished his cycles of the R-CHOP. The patient had a very good overall response to treatment and has currently a relapse of the disease. This presents the ongoing challenges of treatment of patients with transformed lymphoma. CHOP-like chemotherapy has been shown to fail to control lymphoma for the majority of these patients [5]. Rituximab maintenance for 2 years after immunochemotherapy as first-line treatment for follicular lymphoma has been shown to improve progression free survival significantly [8]. Rituximab maintenance improves the quality of response in patients with previously untreated follicular lymphoma that is responsive to first-line rituximab plus chemotherapy [8].

## References

1. [No authors listed] (1997) A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 89: 3909-3918.
2. Qazi R, Aisenberg AC, Long JC (1976) The natural history of nodular lymphoma. *Cancer* 37: 1923-1927.
3. Hubbard SM, Chabner BA, DeVita VT Jr, Simon R, Berard CW, et al. (1982) Histologic progression in non-Hodgkin's lymphoma. *Blood* 59: 258-264.
4. Lossos IS, Gascoyne RD (2011) Transformation of follicular lymphoma. *Best Pract Res Clin Haematol* 24: 147-163.
5. Al-Tourah AJ, Gill KK, Chhanabhai M, Hoskins PJ, Klasa RJ, et al. (2008) Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *J Clin Oncol* 26: 5165-5169.
6. Yuen AR, Kamel OW, Halpern J, Horning SJ (1995) Long-term survival after histologic transformation of low-grade follicular lymphoma. *J Clin Oncol* 13: 1726-1733.

- 
7. Montoto S, Davies AJ, Matthews J, Calaminici M, Norton AJ, et al. (2007) Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol* 25: 2426-2433.
  8. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, et al. (2011) Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *377*: 42-51.