

## CASE REPORTS

## “Triple-triple” hit lymphoma

Sarah Mushtaq<sup>1</sup>, Eric K. Singhi<sup>1</sup>, Robert K. Stuart<sup>2</sup>

1. College of Medicine, Medical University of South Carolina, Charleston SC, USA. 2. Department of Medicine-Division of Hematology and Oncology, Medical University of South Carolina, Charleston SC, USA

**Correspondence:** Robert K. Stuart. Address: 86 Jonathan Lucas St, Charleston, SC 29425, USA. Email: stuartrk@muscc.edu

**Received:** September 9, 2015

**Accepted:** October 27, 2015

**Online Published:** October 30, 2015

**DOI:** 10.5430/crim.v2n4p78

**URL:** <http://dx.doi.org/10.5430/crim.v2n4p78>

### Abstract

Triple-hit lymphoma is a rare but serious form of Non-Hodgkin's lymphoma that is known to have a worse prognosis than diffuse large B-cell lymphoma (DLBCL) or Burkitt lymphoma (BL) alone, with a survival time of only a few months. A triple-hit lymphoma has cytogenetic abnormalities consistent with chromosomal rearrangements of the BCL-6, BCL-2, and c-MYC genes, with MYC translocations having a worse prognosis. This specific type of lymphoma is medically challenging to treat, as standard chemotherapy is often ineffective. We report a case of a 47-year-old African American male with triple-hit lymphoma as a result of a series of progressive malignant transformations over a time course of three years.

### Keywords

Triple hit lymphoma, Chromosomal gene rearrangements

## 1 Introduction

Lymphoma is defined as a cancer involving the malignant transformation of lymphocytes. There are two main types of a lymphoma: Hodgkin lymphoma and Non-Hodgkin lymphoma (NHL). NHL is more common, with diffuse large B-cell lymphoma being one prominent form of NHL. B-cell lymphomas involve chromosomal gene rearrangements, which can result in varying cytogenetic abnormalities that dictate how malignant the lymphoma will be. Double-hit lymphoma is an aggressive lymphoma characterized by two chromosomal rearrangements involving BCL-2 and MYC translocations, which carries a poor prognosis <sup>[1]</sup>. World Health Organization (WHO) classification from 2008 lists this lymphoma as “B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL)” <sup>[2]</sup>. Triple-hit lymphomas are an even more rare and aggressive form of NHL. A triple-hit lymphoma has cytogenetic abnormalities consistent with chromosomal rearrangements of BCL-6, BCL-2, and c-MYC genes, which also results in features between DLBCL and BL. Triple-hit lymphomas have a poorer prognosis than double-hit lymphomas and either DLBCL or BL <sup>[3]</sup>. We present a case of a patient presenting with mandibular swelling, epistaxis, and lower back pain on three separate occasions respectively. Ultimately, after his third presentation cytogenetics confirmed triple-hit lymphoma.

## 2 Case presentation

A 47-year-old African American male presented to his primary care physician in 2012 with a three-month history of mandibular swelling. He was found to have a conglomerate of lymph nodes extending from his mandible to his supraclavicular area bilaterally. He was given antibiotics but despite treatment, the patient's swelling did not resolve. He was referred to a surgeon for excisional biopsy of a node on the right side of his neck which revealed destruction of normal architecture with closely packed poorly demarcated follicles without mantles. Flow cytometry was remarkable for CD20+ BCL2+ BCL6+ CD5-. The pattern was most consistent with 75% follicular lymphoma stage 3, grade 1. The patient elected to undergo six months of bendamustine and rituximab and was found to be in remission in January 2013.

Several months later, the patient presented to the emergency department with a new complaint of epistaxis and mucosal bleeding after a tooth extraction procedure. At this time, he was found to be pancytopenic and was subsequently diagnosed with a double-hit lymphoma, consistent with BCL-2 and MYC mutations, which had transformed from the previous follicular lymphoma. The patient was started on hyper CVAD/HDMTX and ARAC  $\times$  four courses. At the time of count recovery, bone marrow results were concerning for minimal residual disease. Marrow was repeated two weeks later and revealed a relapse of ALL. He was then admitted for HAM salvage and received conditioning with myeloablative cytoxan and TBI. A stem cell transplant with donor cells was performed in 2014.

One month later, the patient presented with a complaint of sciatica like pain, extending from the lower back to his lower extremities. The patient underwent CT imaging and a biopsy was taken of the paralumbar mass, which revealed a diffuse large B-cell (DLBC) triple-hit lymphoma with c-MYC, t (14: 18), and BCL-6 mutations. The patient was then started on treatment with rituximab, gemcitabine, and oxaliplatin.

## 3 Discussion

The inherent nature of a lymphoma is secondary to key chromosomal rearrangements that allow for unregulated cell growth and division. For example, a follicular lymphoma is characterized by a translocation of chromosome 14 (IgH) and chromosome 18 (BCL-2), thus leading to increased transcription of a fusion protein and upregulation of anti-apoptotic characteristics<sup>[4]</sup>. Chromosomal duplication or translocation of the c-MYC gene can lead to enhanced expression in tumor cells, which allow tumor cells to override the p53-regulated cell cycle arrest signal<sup>[5]</sup>. Having two chromosomal rearrangements classifies the lymphoma as a double-hit lymphoma that is clinically uncommon. Double-hit lymphomas are accompanied by an aggressive disease course and are less responsive to therapeutic interventions. The incidence for double-hit lymphomas is 2% of B-cell lymphomas<sup>[6]</sup>. It is important to note that as discussed in the WHO classification of tumors of hematopoietic and lymphoid tissues, it is rare that patients with follicular lymphoma experience a transformation to B-ALL. Most of these cases appear to represent blast transformation of the original B-cell tumor.

Triple-hit lymphomas are a unique form of a lymphoma and are clinically very rare. The incidence of this type of lymphoma is currently unknown, with very few case reports in the literature. Triple-hit lymphomas contain three chromosomal rearrangements of the BCL-6, BCL-2, and c-MYC genes<sup>[7]</sup>. Mutations of the BCL-6 gene can lead to tumor progression secondary to the repression of the p53 signal<sup>[8]</sup>. Triple-hit lymphomas are also well known for having a tumultuous disease course given their spread to extranodal sites on a more frequent and rapid basis<sup>[9]</sup>. Triple-hit lymphomas have a poor prognosis as compared to other types of lymphoma, with an average survival time of four months<sup>[9]</sup>. Standard chemotherapy is often ineffective for the treatment of triple-hit lymphomas. Treatment for advanced disease is chemotherapy in combination with immunotherapy.

This case report highlights the unique course of genetic transformations over a three-year course that resulted in the diagnosis of a triple-hit lymphoma. We believe that this case report is an illustrative case that highlights the genetic instability of lymphomas in general, and the potential for transformation of malignant lymphomas. Our hope is raise

awareness of this rare disease process in order to promote further research in this field that focuses on early detection and treatment of triple-hit lymphomas.

## Acknowledgements

We would like to acknowledge Dr. Robert Stuart for his continued mentorship and support throughout this case. We would also like to acknowledge Dr. Deborah DeWaay for her mentorship and guidance.

## References

- [1] Snuderl M, Kolman OK, Chen YB, *et al.* B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. *Am J Surg Pathol.* 2010; 34(3): 327-340. PMID:20118770 <http://dx.doi.org/10.1097/PAS.0b013e3181cd3aeb>
- [2] Campo E, Swerdlow SH, Harris NL, *et al.* The 2008 WHO Classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood J.* 2011; 117(19): 5019-5032. PMID:21300984 <http://dx.doi.org/10.1182/blood-2011-01-293050>
- [3] Cuneo A, Castoldi G. Follicular lymphoma (FL). *Atlas Genet Cytogenet Oncol Haematol.* 2001; 5(2): 125-126.
- [4] Pemmaraju N, Gill J, Gupta S, *et al.* Triple-hit lymphoma. *Proc (Bayl Univ Med Cent).* 2014; 27(2): 125-127. PMID:24688198
- [5] de Jong D. Novel lymphoid neoplasms-the borderland between diffuse large B-cell lymphoma and Burkitt's lymphoma. *Haematologica.* 2009; 94(7): 894-896. PMID:19570750 <http://dx.doi.org/10.3324/haematol.2009.008128>
- [6] Atkin NB. MYC (v-myc myelocytomatosis viral oncogene homolog (avian)). *Atlas Genet Cytogenet Oncol Haematol.* 2000; 4(4): 181-182.
- [7] Xu X, Zhang L, Wang Y, *et al.* Double-hit and triple-hit lymphoma arising from follicular lymphoma following acquisition of MYC: report of two cases and literature review. *Int J Clin Exp Pathol.* 2013; 6(4): 788-794. PMID:23573328
- [8] Phan RT, Dalla-Favera R. The BCL6 proto-oncogene suppresses p53 expression in germinal-centre B cells. *Nature.* 2004; 432(7017): 635-9. PMID:15577913 <http://dx.doi.org/10.1038/nature03147>
- [9] Motlló C, Grau J, Juncà J, *et al.* Translocation (3; 8) (q27; q24) in two cases of triple hit lymphoma. *Cancer Genet Cytogenet.* 2010; 203(2): 328-332. PMID:21156254 <http://dx.doi.org/10.1016/j.cancergencyto.2010.08.018>