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Prediction of Immunoglobulin/*c-myc t(8;14)* Gene Translocation in Burkitt Lymphoma by Immunohistochemistry

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ABSTRACT

Background: Endemic Burkitt lymphoma (eBL) is a common and aggressive childhood cancer in East and Central Africa. Confirming the diagnosis using molecular tests, such as immunoglobulin (Ig)/*c-myc t(14;8)* gene translocation is difficult in many low-resource settings. This study aimed to examine whether a simpler laboratory method, immunohistochemistry (IHC) for MYC protein, could reliably predict the presence of the Ig/*c-myc, t(14;8)* gene translocation in tumors from children with eBL treated at a referral hospital in Western Kenya.

Materials and Methods: Tumor tissue samples from 22 children and adolescents (≤18 years) diagnosed with eBL in 2013 were randomly selected from hospital block archives. MYC protein expression was assessed using IHC on thin tissue sections, while the presence of the Ig/*c-myc t(14;8)* gene translocation was confirmed using both IHC and fluorescence in situ hybridization (FISH). Demographic and clinical information were obtained from hospital records and structured interviews.

Results: About one quarter of the reviewed cases were confirmed as eBL by both IHC and FISH. Most (78.8%) of these cases were boys, with an average age of 8.8 years. A high level of agreement (86.7%) was observed between MYC protein detection by IHC and the presence of the Ig/*c-myc t(14;8)* gene translocation by FISH. This showed that MYC by IHC closely reflects the underlying Ig/*c-myc t(14;8)* genetic change in the studied tumors. Children whose tumors showed MYC abnormalities tended to have poorer treatment outcomes (r=0.344).

Conclusion: Detecting MYC protein using IHC is a reliable and practical way to predict the presence of the Ig/*c-myc t(14;8)* translocation in eBL tumors. When used together with other tumor markers, MYC by IHC can improve diagnostic accuracy and help guide timely treatment decisions in low- and middle-income countries.

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Introduction

Burkitt lymphoma (BL) is an aggressive and fast-growing cancer of B lymphocytes. It occurs in two main forms. The endemic form, endemic Burkitt lymphoma (eBL), is common in parts of East and central Africa, where Epstein–Barr virus (EBV) infection and malaria are widespread. The sporadic form, sporadic Burkitt lymphoma (sBL), occurs around the world and is not strongly linked to infections [1].

In Kenya, lymphomas make up a significant part of the overall cancer burden, accounting for about 8.5% of all cancers and nearly half of cancers in children and adolescents. Most of these are B-cell non-Hodgkin lymphomas [2]. Endemic BL commonly affects areas outside the lymph nodes, especially the jaw, head and neck, kidneys, digestive tract, ovaries, and sometimes the breast [3]. Jaw tumors are usually seen in younger children, while abdominal disease tends to be more common in older children and teenagers. In the sporadic form, the disease often involves the abdominal illeocecal lymph node, characterized by enlargement of the affected lymph nodes, especially in adolescents [4].

At the genetic level, eBL is driven by changes involving the *c-myc* gene, which regulates the synthesis of myelocytomatosis (MYC) protein [5]. This MYC protein plays a key role in controlling how a cell grows, divides, and undergoes programmed cell death. In most cases of BL, the *c-myc* gene on chromosome 8 is moved next to highly active immunoglobulin gene regions on chromosomes 14, 2, or 22, leading to rearrangements denoted as immunoglobulin (Ig)/*c-myc t(8;14)*, Ig/*c-myc t(2;14)*, and Ig/*c-myc t(8;22)*, respectively. These rearrangements to highly active chromosome regions cause the *c-myc* gene to become permanently 'switched on', especially during immune responses to infections, such as Epstein–Barr virus (EBV) and Plasmodium malariae [6].

When the *c-myc* gene is continuously activated, MYC protein synthesis is upregulated and accumulates, and the affected cells begin to divide excessively, leading to neoplasia. This happens because this protein increases the activity of enzymes that drive cell division and suppresses the natural control of the cell cycle. As a result, normal processes such as cell maturation, repair, and programmed cell death are disrupted, leading to cancer formation, particularly in areas where exposure to infections is common [7]. Genetic changes are beneficial for diagnosing and predicting the behavior of lymphomas [8]. The Ig/*c-myc t(14;8)* is the most common gene translocation usually found in Burkitt lymphoma but rarely in other lymphomas [9]. However, multiple genetic aberrations may concurrently occur in some lymphomas [10].

In many hospitals in East and central Africa, including Kenya, lymphoma diagnosis still relies mainly on routine microscope examination of hematoxylin and eosin (H&E) stained sections. However, several aggressive B-cell lymphomas look very similar to eBL under the microscope, making it difficult to make an accurate diagnosis based only on appearance [11, 12]. According to the World Health Organization (WHO) guidelines, immunohistochemistry (IHC) and molecular tests are now required to correctly diagnose eBL. Detection of the Ig/*c-myc t(14;8)* translocation is included [13].

Relying only on tissue microscopic appearance can lead to misdiagnosis and affect timely treatment decisions [14]. For this reason, this study aimed to evaluate MYC protein expression using IHC to determine the Ig/*c-myc t(14;8)* translocation as detected by fluorescence in situ hybridization (FISH) in tumor tissue samples from children with eBL at a referral hospital in western Kenya.

Materials and Methods

This study analyzed 22 archived tumor tissue blocks randomly selected from 33 previously confirmed eBL cases who sought care at Moi Teaching and Referral Hospital in Western Kenya. All patients were children or adolescents aged ≤18 years and had not yet started chemotherapy at the commencement of this study and before biopsies were taken in 2013. The study was approved by the hospital's Institutional Scientific and Research Ethics Committee. Written consent was obtained from each parent or legal guardian before recruitment.

The tissue sections collected were stained using routine hematoxylin and eosin (H&E) staining and a selected panel of IHC antibodies, including anti-MYC, based on a previous study protocol [15]. More than one specialist pathologist examined each slide independently to arrive at an eBL diagnosis. When there were differences in interpretation, the particular cases were reviewed by the pathologists together using a multi-headed microscope until an agreement was reached. Samples with poor tissue quality or preparation were excluded.

To detect MYC protein, thin tissue sections were processed by removing wax, rehydrating the tissue, and retrieving antigens using a heat-based method in citrate buffer. Endogenous enzyme activity was first blocked, and then staining was performed using the standard

3,3-diaminobenzidine chromogen-based detection system, following the manufacturer's instructions (DAKO, Milan, Italy).

To detect the Ig/*c-myc t(14;8)* translocation, FISH testing was performed using commercially available dual-color break-apart probes. The tissue sections were prepared through a series of heating, washing, and enzyme digestion steps to allow the probe to bind effectively. The sample slides were then incubated overnight with the probe for hybridization. After which, the slides were washed, counterstained with fluorescent dye 4,6-diamidino-2-phenylindole, and examined under a fluorescence microscope. At least 100 cell nuclei were analyzed per case. Normal cells (without target translocation) showed two fused signals, while cells with the translocation showed split red and green signals. All results were reviewed independently by at least two specialist pathologists to minimize bias.

Clinical and demographic information, including age, sex, and tumor location, were obtained from hospital records and structured interviews with parents and/or legal guardians during subsequent visits to the hospital.

Results

Out of the 33 patients diagnosed and with tissue blocks during the study period, 22 tissue blocks were picked and deemed suitable for detailed analysis in this study. Most of the patients were boys (79%), and the average age at diagnosis was 8.8 years. Tumors were mainly located in the jaw and the abdomen.

A strong agreement was found between MYC protein expression detected by IHC and Ig/*c-myc t(14;8)* translocation detected by FISH. About 86.7% of the cases were positive by both methods (Table 1). A small proportion of eBL tumors (13.3%) did not show MYC protein expression by IHC but still carried the Ig/*c-myc t(14;8)* translocation by FISH (Figure 1). When MYC expression was compared with clinical outcomes within the year of this study, cases with MYC expression abnormalities tended to have poorer treatment outcomes (correlation coefficient r=0.344).

Discussion

This study found eBL to be more common in boys than girls, which is consistent with reports from other African regional settings [16]. The higher male-to-female ratio compared to some studies [17] may be due to gender-based physiological differences, environmental and/or social factors which influence lymphoma development.

Abdominal tumors were more common than jaw tumors in this study, which agrees with findings from northern Uganda and Ghana in East and West Africa, respectively [18, 19]. This finding appears to suggest that the pattern of how BL presents is changing over time. It may also be that the recent improvements in surgical techniques to obtain abdominal samples and diagnostic capacity are allowing better recognition of abdominal disease.

The strong match between MYC protein expression and FISH results shows that IHC can be a reliable tool for identifying MYC-driven BL, consistent with Tapia et al. [20]. The small number of FISH-positive but IHC-negative cases suggests that some tumors may develop through alternative genetic pathways, or that they do not strongly express MYC protein despite having gene rearrangements.

The finding that MYC abnormalities were linked to worse treatment outcomes supports the potential of MYC status being used for prognosis in eBL patients from the study region. Differences from other studies may relate to possible differences in treatment protocols or patient populations involved in those studies.

Table 1. Percentage detection of Ig/*c-myc t(14;8)* gene translocation by IHC and FISH

IHC-MYC	FISH Ig/*c-myc t(14;8)*	
	% -ve	% +ve
% +ve	50	87
% -ve	50	13
Total (%)	100	100

Abbreviations: Ig: Immunoglobulin; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization.

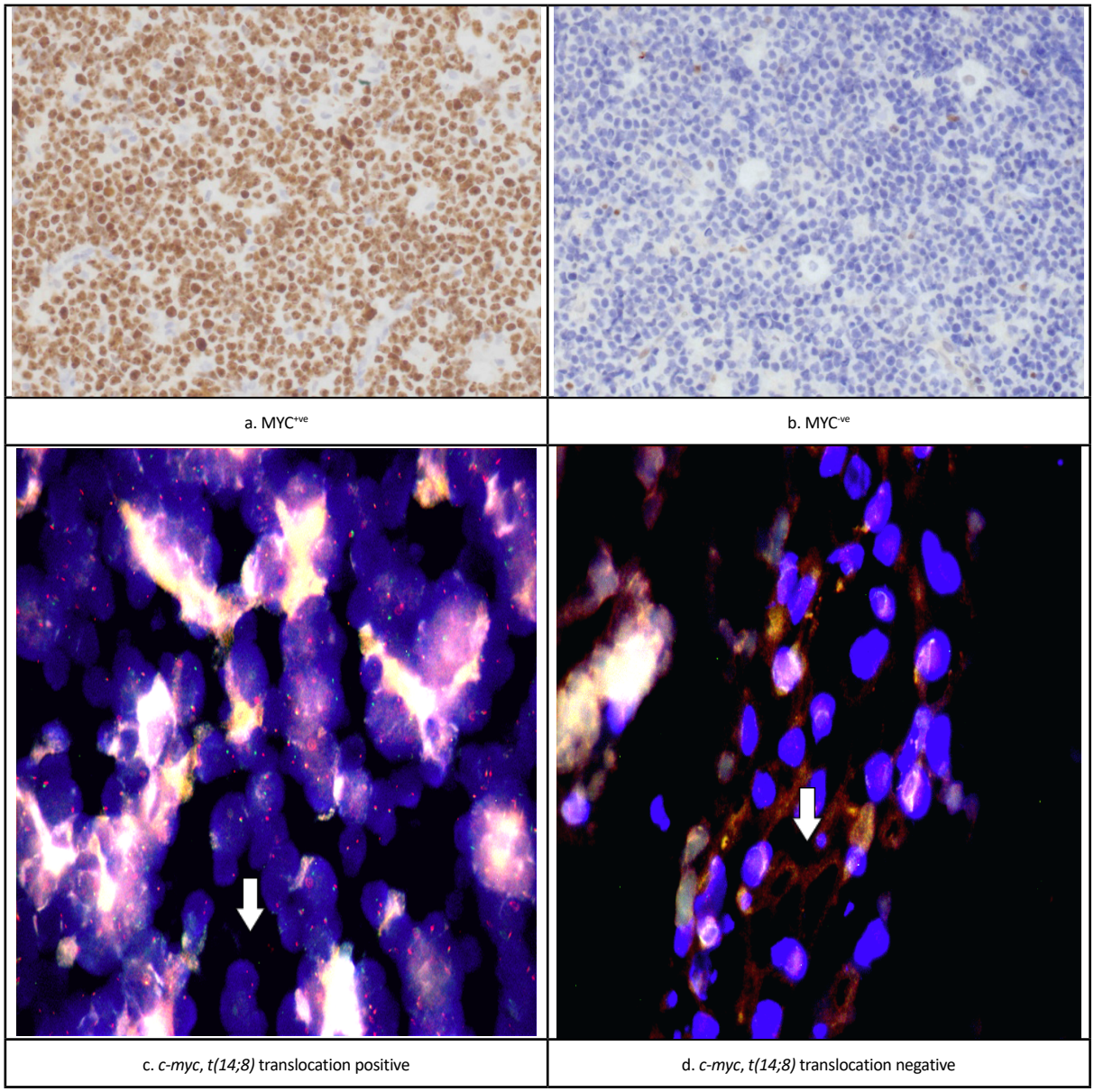


Figure 1. Representative slides

a and b) IHC stained myelocytomatosis (MYC+/-); c and d) FISH cellular myelocytomatosis (*c-myc*) *t(14;8)* translocation +v

Note: Red-green juxtaposed signal positive for Ig/*c-myc*, *t(14;8)* translocation, split signal negative.

Conclusion

Detecting MYC protein using IHC is a practical and affordable way to identify Ig/*c-myc t(14;8)* gene rearrangements in lymphomas, especially in resource-limited settings. Using IHC alongside routine tests can improve diagnostic accuracy of eBL and help guide timely treatment decisions. Abnormalities involving MYC are linked to poorer outcomes and can be used as important prognostic markers. Further studies should explore other genetic changes that may improve diagnosis and treatment outcomes.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in studies involving human participants were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments as set out in the ethical standards of the Moi University/Moi Teaching and Referral Hospital Institutional Scientific and Research Ethics Committee.

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Authors contribution's

Study design, acquisition, analysis, and data interpretation: Isaac Ndede, Simeon K. Mining, and Kirtika Patel; Data collection: Fredrick M. Wanjala, Constance Tenge, and David Chumba; Analysis, data interpretation, investigation, writing, and final approval: All authors.

Conflict of interest

The authors declared no conflict of interests.

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