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CASE REPORT

“In situ” *MYC* rearrangement and amplification as a secondary change in a case of High-grade B cell lymphoma with 11q aberration

Gioia Di Stefano[1] · Susanne Bens[2] · Anja Fischer[2] · Manuel Ciceri[3] · Luca Nassi[3] · Reiner Siebert[2] · Raffaella Santi[4]

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Abstract

High-grade B cell lymphoma with 11q aberration (HGBCL-11q) is an aggressive lymphoma with a germinal center (GC) B cells phenotype. It is characterized by a cytogenetic alteration on the long arm of chromosome 11, which includes proximal gains and telomeric losses. HGBCL-11q shares certain morpho-phenotypic and gene expression features with Burkitt lymphoma (BL) but lacks the typical *IG::MYC* translocation. The current classifications consider HGBCL-11q as *MYC* rearrangement negative lymphoma. In contrast, in BL the characteristic 11q aberration is recognized as a secondary event occurring during clonal evolution. An increasing number of aggressive GC B cell lymphomas exhibiting both the typical 11q aberration and *MYC* rearrangement at the initial diagnosis are reported mostly as HGBCL, NOS (not otherwise specified). However, there is limited data on the temporal relationship between *MYC* rearrangement and the 11q aberration in these instances. Here, we present a case of nodal HGBCL-11q that shows a focal area with elevated *MYC* protein expression and a copy number gain of a rearranged *MYC* locus. These findings suggest that *MYC* rearrangement can occur as a secondary event in HGBCL-11q.

Keywords High-grade B cell lymphoma with 11q aberration · MYC · Burkitt lymphoma · High-grade B cell lymphoma

Introduction

High-grade B cell lymphoma with 11q aberration (HGBCL-11q) according to the 5th edition of the World Health Organization (WHO-HAEM5) classification (corresponding to large B-cell lymphoma with 11q aberration according to the International Consensus Classification (ICC)) is an aggressive mature B cell lymphoma expressing germinal center (GC) B cell markers [1–3]. It shows many similarities to Burkitt lymphoma (BL) in terms of morphology, gene expression, and phenotype but differs strongly from BL with regard to genomic alterations. Concerning structural genomic variants, HGBCL-11q is characterized by a recurrent cytogenetic alteration on the long arm of chromosome 11 consisting of a proximal gain (11q23.2q23.3) and a telomeric loss (11q24.1qter), which is characteristic for HGBCL-11q [1, 4–5]. Since its original description, HGBCL-11q has been defined as a *MYC* rearrangement negative B cell lymphoma [4–6] and, accordingly, cases presenting with concomitant *MYC* rearrangements have been excluded. This definition has been maintained by the WHO-HAEM5 classification [1] aiming to clearly separate HGBCL-11q apart from *IG*::*MYC* positive BL in which other alterations in 11q can occur as a secondary change at the relapse or during progression due to emerging karyotypic complexity [7]. In HGBCL-11q *MYC* gene expression is usually lower than in BL [4] even though *MYC* alterations, in particular copy number gains, have been repeatedly reported [4, 8–9]. These findings suggest that *MYC* copy number alterations along with typical aberrations on the long arm of chromosome 11 may, at times, coexist. The biological and clinical impact of this coexistence is still unclear. It is important to distinguish between cases with

✉ Raffaella Santi
raffaella.santi@unifi.it

1 Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy

2 Institute of Human Genetics, Ulm University and Ulm University Medical Center, Ulm, Germany

3 Hematology Unit, Careggi Hospital and University of Florence, Florence, Italy

4 Pathology Section, Department of Health Sciences, University of Florence, Florence L.go Brambilla, 3, 50134 Florence, Italy

concurrent 11q aberration and *MYC* gain from those with 11q aberration associated with *MYC* rearrangement at the time of the initial diagnosis. Although the latter has been reported occasionally [10], there is still no broad consensus on how to classify these cases.

While for BL the appearance of 11q aberration secondary to *IG*::*MYC* juxtaposition has been documented [7] hardly any data on the timing of *MYC* rearrangement and 11q aberration in HGBCL-11q exist. Herein, we describe a case of nodal HGBCL-11q that exhibits a focal area in which increased MYC protein expression is associated with copy number gain of a rearranged *MYC* locus, thus suggesting *MYC* alterations to occur secondary to 11q aberration in HGBCL-11q.

Case report presentation

A 71-year-old male patient was referred to our institution for a second opinion on a nodal Diffuse large B cell lymphoma (DLBCL), at onset of the disease, also including histopathological re-evaluation. At microscopic examination, nodal architecture was effaced by a diffuse proliferation of medium to large-sized cells with nuclear features mostly recalling blastoid cells (Fig. 1A). Mitotic activity was brisk, and a "starry sky" pattern was occasionally seen. At the periphery, residual follicular structures with preserved GC were also observed. By immunohistochemistry, the lymphoid population showed a GC B cell phenotype (CD20+, CD10+, BCL6+) with a high proliferation rate (Ki-67: 90%) (Fig. 1B, C). BCL2, MUM1, CD5, CD23, LMO2 and Cyclin D1 staining as well as EBER in situ hybridization tested negative. Remarkably, MYC staining was positive in 20–30% of cells with weak to moderate intensity in a single area of the lymph node with no other differences on morphologic and phenotypic grounds compared to the overall lymphoid population (Fig. 1E, F).

FISH was performed using a set of commercial (Abbott/VysisLSI MYC Dual Color Rearrangement probe and LSI IGH/MYC/CEP8 Tri-Color Dual Fusion probe, Abbott Molecular, IL, USA; Leica/IVD BCL2 (18q21) Break-XL for BOND and Leica/IVD BCL6 (3q27) Break-XL for BOND, Leica Biosystems, IL, USA; ZytoLight SPEC 11q gain/loss Triple Color Probe (PL174), Zytovision GmbH, Germany) or recently described non-commercial probes (IGK/MYC and IGL/MYC dual color dual fusion probes [11–12], 11q probe (modified from [4] containing the clones RP11-629A20 (11q24.3) labelled in spectrum orange, RP11-414G21 (11q23.3) labelled in spectrum green and a commercially available chromosome enumeration probe labelled in spectrum aqua as control (CEP11, D11Z1 from Abbott/Vysis, Wiesbaden, Germany)). The results showed the typical 11q aberration pattern with proximal gain in the 11q23 region and a telomeric loss in the 11q24 region across the whole tumor area. Using break-apart (BAP) probes no *BCL2* or *BCL6* rearrangements were observed. The majority of the tumor cells showed three copies of the *MYC* locus without evidence of a translocation. Nevertheless, in the focal area where MYC protein expression was increased, we observed regularly one to three colocalized signals for the MYC BAP probe and, in addition, two "cloud-like" large red signals for the centromeric part of the MYC BAP probe without any juxtaposed green signal (Fig. 2E). This pattern indicates amplification of a rearranged *MYC* locus. We did not detect any *IGH*::*MYC*, *IGK*::*MYC* or *IGL*::*MYC* fusion using dual-fusion tests. A copy number variation (CNV) analysis was performed using OncoScan technology, and the data was analyzed using Chromosome Analysis Suite Software version 4.0 (Thermo Fisher Scientific, Waltham, MA, USA). The analysis confirmed the presence of the typical 11q aberration and *MYC* gain (Fig. 2A-C). Additionally, a subclonal focal copy number gain of the *MYC* locus was noticed, consistent with the patterns observed using FISH. Therefore, we rendered a diagnosis of HGBCL-11q that displayed based on cytogenetic analysis an "in situ" amplification of a rearranged *MYC* gene locus associated with elevated MYC protein.

Exome sequencing and subsequent filtering (likely) protein changing variants with a minor allele frequency (gnomAD exome ALL) of ≤ 1% in 52 genes in which mutations are enriched in HGBCL-11q [5, 13], BL [14] or DLBCL [15] were performed. By this approach we uncovered alterations of *ETS1*, *KMT2D*, *CREBBP*, *EP300*, *TTN*, *TP53*, *P2RY8*, *TBL1XR1* and *PLEC*, i.e. of genes recurrently mutated in HGBCL-11q or DLBCL, but not of *ID3*, *TCF3* or *CCND3* typically found mutated in BL.

After staging with whole-body CT, PET scan, and bone marrow biopsy, the involvement of supra- and infra-diaphragmatic lymph nodes, spleen, and Waldeyer (tonsils) determined a stage IV A. The IPI was 2 (age, stage) and no immunodeficiency status was identified. The patient then underwent an induction treatment with R-COMP (rituximab, cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin, prednisone) for six cycles, associated with central nervous system (CNS) relapse prophylaxis with intrathecal methotrexate during R-COMP and intravenous high-dose methotrexate which is current practice in our center for HGBCL patients, regardless of stage and IPI. The treatment was well tolerated and led to a complete metabolic response according to Lugano criteria.

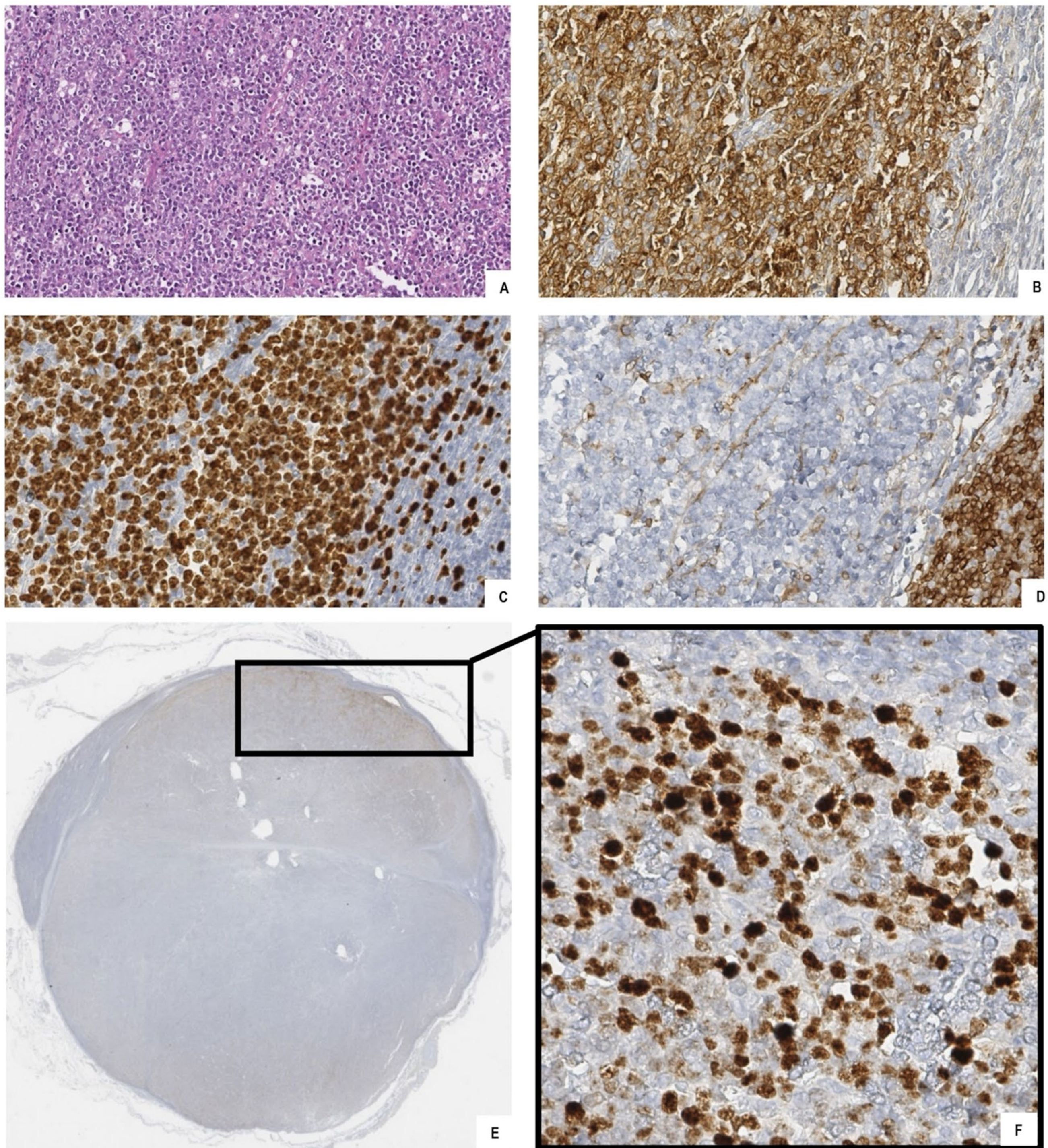
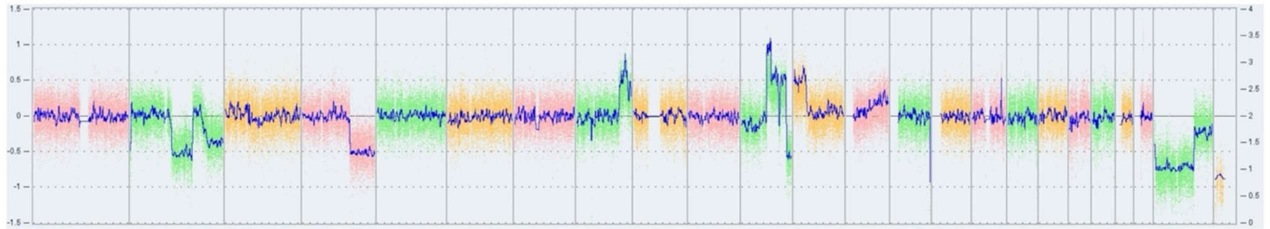
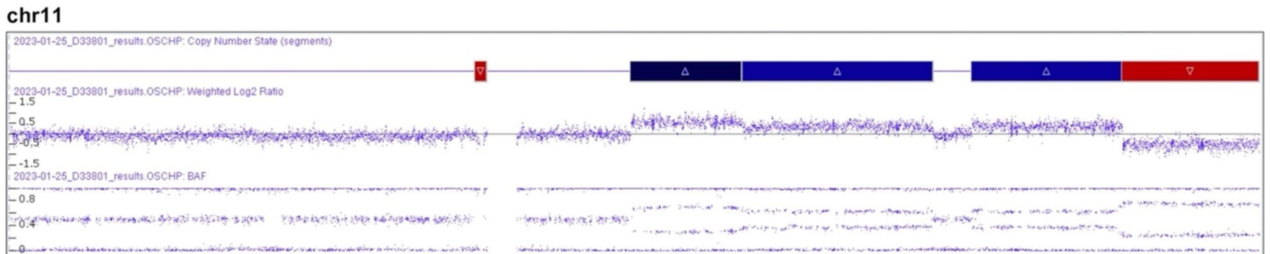


Fig. 1 Morpho-phenotypic features. (**A**) Diffuse proliferation of medium to large-sized cells with nuclear features mostly recalling blastoid cells displaying a brisk mitotic activity and an occasional "starry sky" pattern (hematoxylin-eosin, original magnification 20x). The lymphoid B cell population was positive for germinal center markers like CD10 (**B**) (original magnification 40x) with a high proliferation rate (**C**) (original magnification 40x) but negative for BCL2 (**D**) (original magnification 40x). (**E**) MYC was variably low expressed in the neoplastic lymphoid population (original magnification 2x), with a single area (**F**) showing weak to moderate intensity in 20–30% of the cells (original magnification 20x)

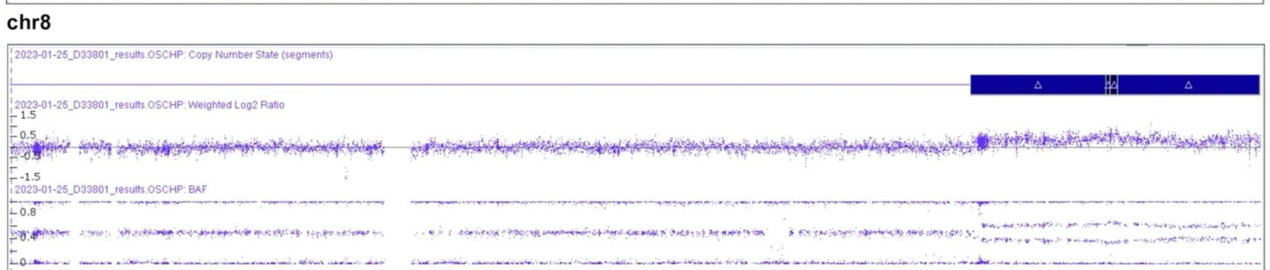
A



B chr11



C chr8



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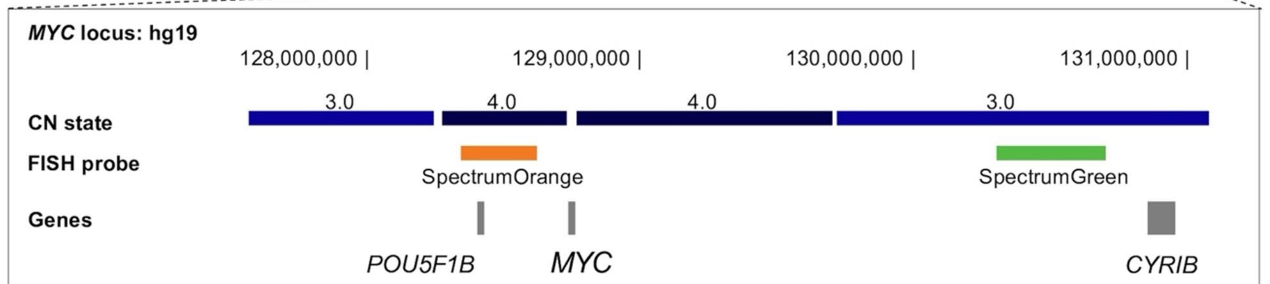

E

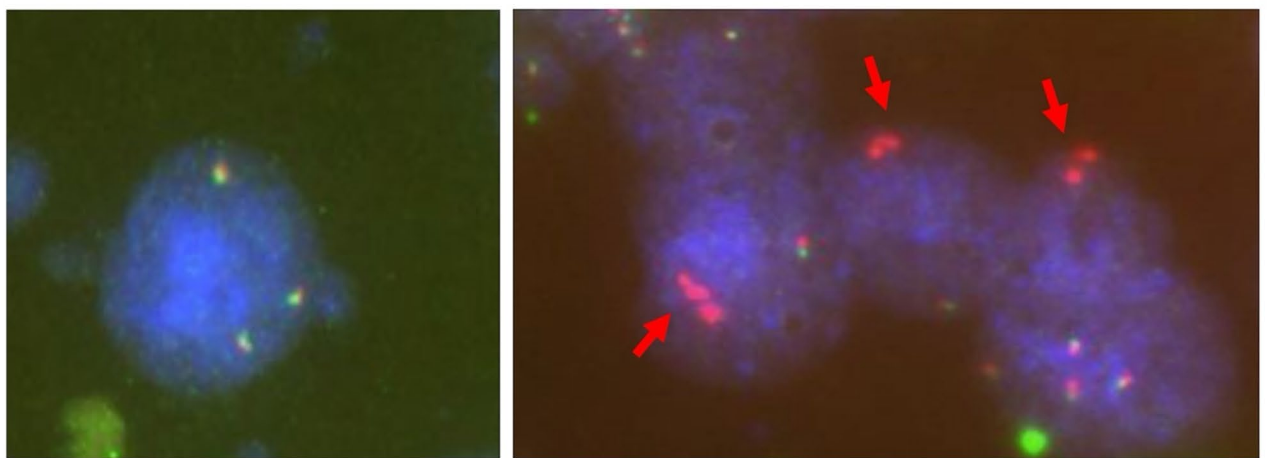

Fig. 2 Copy number and FISH analysis. (**A**) Whole genome copy number profile obtained from an Oncoscan array. Log2 ratio is shown. (**B**) Copy number profile of chromosome 11. Copy number state, weighted log2 ratio and B allele frequency (BAF) is shown. Gains are indicated in blue with shades indicating levels of gains, losses in red. (**C**) Copy number profile of chromosome 8. Copy number state, weighted log2 ratio and B allele frequency (BAF) is shown. Gains are indicated in blue. (**D**) Schematic overview of the *MYC* locus including gains obtained from copy number analysis and the location of FISH probes. (**E**) Left panel: tumor cell with three colocalized signals indicating three copies of *MYC* locus without evidence of a translocation. Right panel: focal area with one to three colocalized signals for the MYC BAP probe and, in addition, two "cloud-like" large red signals for the centromeric part of the MYC BAP probe without any juxtaposed green signal (red arrows). This pattern indicates amplification of a rearranged *MYC* locus. False-color display obtained by ISIS Imaging system (MetaSystems, Altlusheim)

Discussion

Secondary activation of oncogenes via translocations or amplifications are well-known pathogenetic events in lymphoma development and progression. In some instances, for which the term "complicon" has been applied, an oncogene is activated by both rearrangement and amplification, and this mechanism takes place particularly in p53 deficient cells [16], like in the present case. Among the oncogenes recurrently targeted by such changes during lymphoma progression, *MYC* plays a prominent role [1]. Indeed, *MYC* is recurrently activated during the progression of GC origin lymphomas through rearrangement, gains, or a combination thereof. The prototype of GC derived B cell lymphoma with secondary *MYC* activation is Diffuse large B cell lymphoma/High-grade B cell lymphoma with *MYC* and *BCL2* rearrangements (*DLBCL/HGBCL-MYC/BCL2MYC* and *BCL2*), so called "double-hit" lymphoma, in which the partner of the rearranged *MYC* locus is a non-IG locus in roughly half of the cases [1]. In these lymphomas, unbalanced signal patterns upon application of a MYC break apart probe, like the lack of one green signal in the presence of an (amplified) red signal, have been shown to indicate *MYC* rearrangements with typical features like enhancer hijacking in several instances, though it was not proven in the present case [17]. The lymphoma presented herein, thus, provides compelling evidence that *MYC* rearrangement is also a secondary hit in HGBCL-11q. Moreover, the present case indicates that similar to double-hit lymphoma, the *MYC* partner, at least on the level of FISH resolution, might not be an IG-locus in HGBCL-11q. As in bona fide BL with secondary 11q aberration the *MYC* partner would be expected to be an IG locus, the present case can be clearly distinguished from published BL cases with secondary 11q aberration.

In previously published studies on HGBCL-11q where *MYC* gene status as copy number gains were provided, a fraction of cases exhibited this type of gene deregulation, therefore hypothesizing *MYC* copy number gains as a recurrent feature in the evolution of HGBCL-11q [4, 18]. On the other hand, an increasing number of cases of HGBCL-11q with *MYC* rearrangement have been reported at the time of the initial diagnosis, and it has been proposed to classify these cases as HGBCL, not otherwise specified (NOS) [10]. This interpretation is based on certain morpho-phenotypical and mutational features [10] not typically encountered in BL, although further studies are needed to better define these cases. Nevertheless, the exact temporal sequence of these cytogenetic events in most published cases, in contrast to the one presented herein, is unclear.

In summary, we present a case of HGBCL-11q, which is informative for understanding the pathogenesis of these GC derived B cell lymphomas by documenting that *MYC* rearrangement can occur in this entity as a secondary change, that it can involve non-*IG* loci and, moreover, *MYC* amplification, and that these combined changes lead to elevated MYC protein expression compared to the rest of the neoplastic lymphoid population.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Not applicable.

Informed consent Written informed consent was obtained from the patient for the publication of this report and accompanying images.

Competing interests The authors declare no competing interests.

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