

CASE REPORT

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Double-hit lymphoma of the male breast: a case report



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Abstract

Background: Whereas lymphoma of the female breast is already rare, lymphoma of the male breast has only anecdotally been reported. Within a study of 32 lymphoma of the breast reported between 1973 and 2014 as Burkitt lymphoma, we observed a single male case, which we report here.

Case presentation: A 72-years-old Caucasian man presented with a mass in his left breast. Clinical history included prior basal cell carcinoma, leiomyosarcoma, and administration of spironolactone. The reference pathology diagnosis at presentation was Burkitt lymphoma according to the Kiel Classification. The present re-investigation using fluorescence *in situ* hybridization revealed an IGH-MYC translocation and a break in the *BCL2* locus in the tumor cells. Thus, in light of the current WHO classification, the diagnosis was revised to high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement, Burkitt morphology (so-called “double-hit” lymphoma). Genome-wide chromosomal imbalance mapping revealed a complex pattern of aberrations in line with this diagnosis. The aberrations, including copy-number gains in chromosomes 3q and 18 and focal homozygous loss in 9p21.3, resembled typical changes of lymphomas affecting “immune-privileged” sites.

Conclusion: The present case adds to the understanding of the pathogenesis of male breast lymphomas, about which hardly any molecular characterization has been published yet.

Keywords: Lymphoma, *MYC*, *BCL2*, breast, male, Burkitt

Background

Primary lymphoma of the male breast is an extremely rare presentation affecting males in the fourth to seventh decades of life [1, 2]. To date, less than 50 cases of male breast lymphoma have been reported in the literature [1, 2]. Clinical presentation of breast lymphoma in men usually resembles the more common carcinomas with a mammographically solitary well-circumscribed painless mass in the breast and/or the ipsilateral axillary lymph nodes commonly unilateral [3–8]. Previous reports on male breast lymphomas focused mainly on the clinical

and pathological features of the tumor [3–9]. Reports describing the genetic alterations of male breast lymphomas are, to the best of our knowledge, scarce. In the context of a retrospective study aiming at molecularly characterizing 32 lymphomas of the breast diagnosed historically between 1973 and 2014 as Burkitt lymphoma at the Lymph Node Registry in Kiel (Germany), we came across the case of a single male patient, which is presented here.

Case Presentation

The tumor tissue sample of the at diagnosis 72-year-old Caucasian man was obtained at the Lymph Node Registry in Kiel (Germany) more than 25 years ago. His main complaint was an asymptomatic unilateral progressive mass of his left breast persisting over 3 months. A

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history of basal cell carcinoma and leiomyosarcoma was recorded 25 and 10 years prior to the lymphoma manifestation, respectively. Furthermore, long-term treatment with spironolactone was reported. A clinical examination revealed bilateral non-tender gynecomastia along with a painless swelling in his left breast and testis together with ipsilateral enlarged superficial inguinal lymph nodes. Bilateral mastectomy was performed and reference pathological analyses of the excised tissue led at that time to the diagnosis of Burkitt lymphoma of the breast according to the Kiel Classification. Neither data on treatment nor on outcome were available. During a retrospective survey of breast and ovarian lymphomas historically diagnosed as Burkitt lymphoma at the Lymph Node Registry in Kiel (Germany), archived tumor materials (formalin-fixed, paraffin embedded, [FFPE]) of the case described above were retrieved from the files and investigated applying up-to-date technologies. Use of the archived materials for molecular studies was approved by the Ethics Committee of the Faculty of Medicine, Christian-Albrechts-University of Kiel, Germany (D474/14 and D447/10). Interphase fluorescence *in situ* hybridization (FISH) studies were performed using the dual color break apart probes, LSI *MYC*, LSI *IGH*, LSI *BCL2* and LSI *BCL6*, as well as, the tri-color dual fusion probe LSI *IGH/MYC/CEP8* (all probes were obtained from Vysis/Abbott Molecular, Wiesbaden, Germany). Whenever possible at least 100 nuclei were evaluated for each probe. FISH analyses were evaluated and documented using the ISIS digital image analysis version 5.0 (MetaSystems, Altusheim, Germany). For histological evaluation, tumoral tissue was stained with Hematoxylin and Eosin (H&E), as well as with a panel of monoclonal antibodies for detection of CD20, CD10, BCL2, TdT and Ki67 expression. Moreover, Epstein-Barr virus (EBV) encoded RNA (EBER) *in situ* hybridization was performed. For the analysis of genome-wide imbalances, DNA was extracted from the FFPE material with the QIAamp DNA FFPE tissue kit, (Qiagen, Hilden, Germany) and processed using the Oncoscan™ FFPE express 2.0 kit (Affymetrix, Santa Clara, CA, USA). Analyses of copy number aberrations (CNA) and copy neutral loss of heterozygosity (CNN-LOH) were performed using the TuScan algorithm of the Nexus Express for Oncoscan 3 software (Biodiscovery, El Segundo, CA, USA). Human reference genome GRCh37/hg19 was used. Gains and losses smaller than 100 Kb or encompassing less than 20 probes, as well as CNN-LOH smaller than 5000 Kb or including regions of losses were not considered.

Histopathological re-examination showed a diffuse proliferation pattern of malignant medium-sized B-lymphocytes (Fig. 1a), suggestive of mature aggressive B-cell lymphoma of Burkitt type in line with the historic

diagnosis relying on the Kiel Classification. The tumor cells stained positive for CD20 and BCL2 (Fig. 1b and c) but negative for TdT, CD10 and EBER. Ki-67 showed non-representative staining most likely due to the aging effect of the stored material and thus, was considered not evaluable for technical reasons.

Molecular cytogenetic analyses using interphase FISH revealed the vast majority of cells in the tissue section to carry a chromosomal breakpoint affecting the *MYC* locus and an *IGH-MYC* fusion as well as a chromosomal breakpoint affecting the *BCL2* gene locus (Fig. 1d and e). In addition, we detected an extra signal of the non-rearranged allele suggesting a gain of the *BCL2* locus. Moreover, we observed a gain but no break of the *BCL6* locus. Based on these results and in the light of the current World Health Organization (WHO) classification of lymphoma the diagnosis was revised toward “high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements, Burkitt morphology”, commonly referred to as “double-hit lymphoma”.

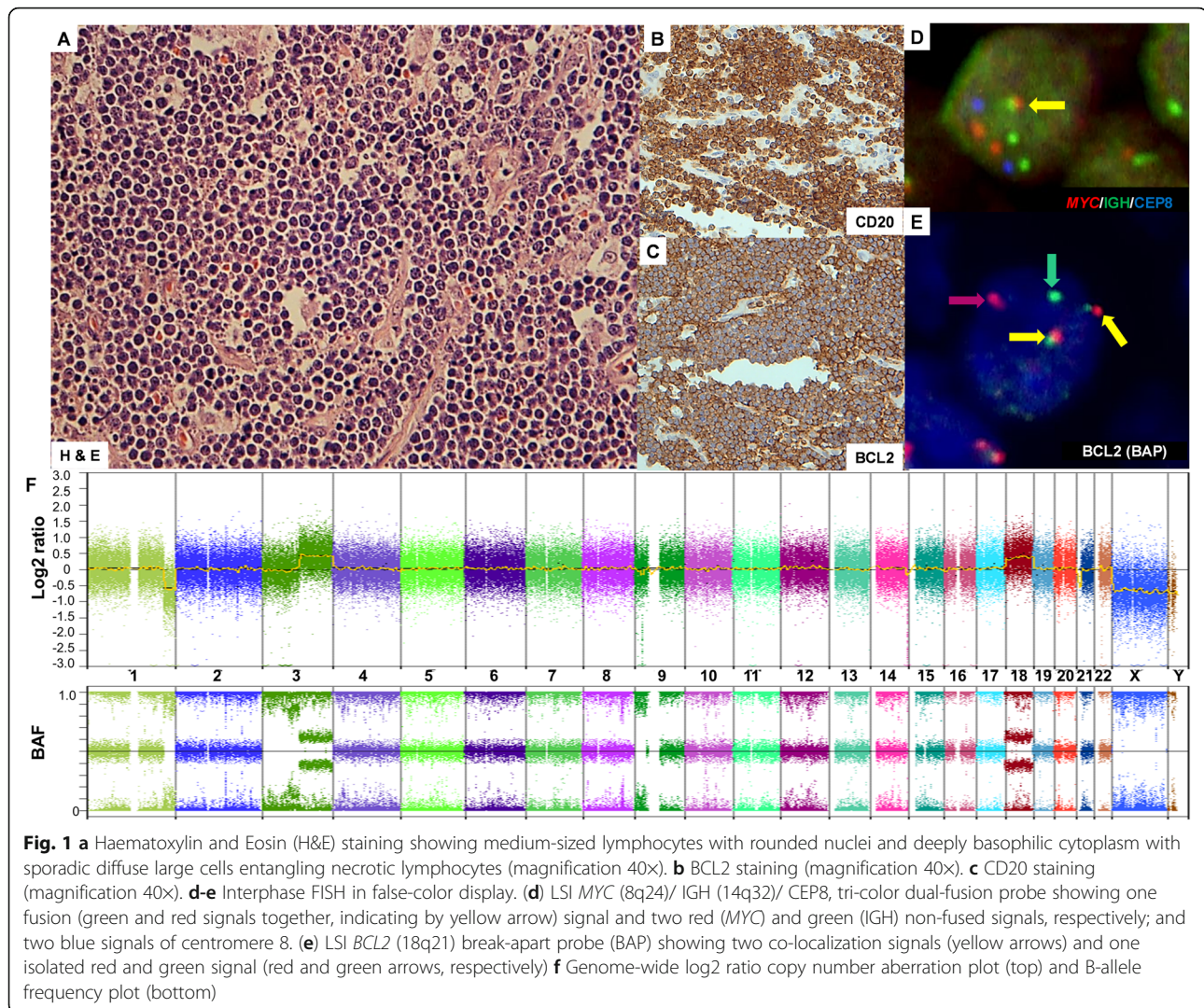
Chromosomal imbalance mapping using the Oncoscan™ platform revealed copy number (CN) gains in 3q13.11-q29 and a trisomy 18 (in line with the observed FISH patterns) and CN losses in 1q41-q44, 2q31.1, 9p21.3, and 10q21.1. Moreover, CNN-LOH were detected in 3p26.3-q13.11, 9p24.3-p13.3, 15q21.1-q21.3, and 16p13.3 (Fig. 1f). Finally, attempts to perform whole-exome sequencing from the tumor unfortunately failed due to technical reasons likely caused by the limited preservation of the historic tissue.

Discussion

Primary lymphoma of the breast is extremely rare. In contrast to female breast lymphoma that is assumed to occur in up to 0.05% of women with breast malignancy [10], presentation of the lymphoma in the male breast has been reported only sporadically in rare cases worldwide [1, 2].

In the few reported male cases, like in the patient presented here, breast lymphoma mainly affected men in the middle-to-old age groups [2–8]. Being initially considered as Burkitt lymphoma, we here rendered the diagnosis of a so-called “high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements” also called “double-hit lymphoma” with Burkitt morphology. This re-classification sets a note of caution to historic studies on the incidence and biology of Burkitt lymphomas in elderly patients or with unusual presentation.

High-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements represent a quite recently defined entity of lymphoma with aggressive nature, high genomic complexity and poor prognosis [9]. Double-hit lymphomas



comprise between 32% and 78% of mature aggressive B-cell lymphoma cases with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma [10, 11].

In line with the diagnosis of double-hit lymphoma the complexity of the genomic imbalances depicted by the Oncoscan™ array was high. The pattern of imbalances showing gains in 3q and trisomy 18 as well as homozygous loss in 9p21.3 (encompassing the region of *CDKN2A/B*) together with the lack of detectable CD10 in the presence of CD20 and BCL2 expression resembles other extra-nodal lymphoma. This holds particularly true for aggressive B-cell lymphomas at immune-privileged sites, like primary CNS lymphomas (PCNSL) or testicular lymphomas [12, 13]. The causes for this rare manifestation in the patient presented here remain unclear. Nevertheless, it is intriguing to speculate that there might be an association with the former spironolactone treatment, well known to induce gynecomastia. Alternatively, based on the clinical history of the patient

with multiple neoplasia, a tumor predisposition syndrome could underly lymphoma development. Unfortunately, we could not investigate the latter hypothesis as the tumor material was of insufficient quality for whole-exome analysis.

Conclusion

In conclusion, we described a rare EBV-negative high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements of the male breast. The similarities of the molecular findings to other types of non-nodal aggressive B-cell lymphoma affecting immune-privileged sites might indicate common pathogenetic mechanisms.

Abbreviations

BCL2: B-cell lymphoma 2; BCL6: B-cell lymphoma 6; CD20, CD10: Cluster of differentiation 20, cluster of differentiation 10 (markers of B-cell maturity); *CDKN2A/B*: Cyclin-dependent kinase inhibitor 2A/B; *CEP8*: Chromosome enumerator probe 8 (Centromeric probe of chromosome 8); CN: Copy number; CNA: Copy number aberration; CNN-LOH: Copy neutral loss of heterozygosity; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus-encoded

RNA; EBV: Epstein-Barr virus; FFPE: Formalin-fixed, paraffin-embedded; FISH: Fluorescence *in situ* hybridization; H & E: Hematoxylin and Eosin; IGH: Immunoglobulin heavy chain; ISIS: name of Software for FISH from MetaSystem; Ki-67: Marker of cell proliferation; Kb: kilobase; LSI: Locus-specific identifier; MYC: Cellular myelocytomatosis gene; NCBI: National Center for Biotechnology Information; PCNSL: Primary central nervous system lymphoma; TdT: Terminal deoxynucleotidyl transferase; USA: United States of America; WHO: World Health Organization

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Footnote

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Authors' contributions

SE identified the case, performed the analyses, and drafted the manuscript. IN reviewed the fluorescence *in situ* hybridization, interpreted data, corrected and approved the manuscript. CL reviewed the fluorescence *in situ* hybridization, interpreted data, corrected and approved the manuscript. SB reviewed the fluorescence *in situ* hybridization, interpreted data, corrected and approved the manuscript. MS reviewed of the histopathological analyses and immunohistochemical staining, interpreted data, corrected and approved the manuscript. RW reviewed the genome-wide copy number data, interpreted data, corrected and approved the manuscript. WK conceived and supervised the study, performed the histopathological review, corrected and approved the manuscript. RS conceived and supervised the study and drafted the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Ethical Committee of the Faculty of Medicine of Christian-Albrechts University of Kiel (number D474/14 with reference to 447/10).

Consent for publication

We declare that the study was performed in accordance with the guidelines of the ethics committee but, based on the historic nature of this case, we cannot provide a signature of patient or relative.

Competing interests

The authors have no competing interest to declare.

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