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Burkitt-like lymphoma with 11q aberration mimicking appendicitis in a young man: a diagnostic and therapeutic challenge

Ryszard Swoboda[1], Karolina Gajda[2], Roman Lamch[2], Sebastian Giebel[1]

[1]Department of Bone Marrow Transplantation and Onco-Haematology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland

[2]Tumor Pathology Department, Molecular Pathology Laboratory, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland

Abstract

Burkitt-like lymphoma with 11q aberration (BLL-11q) is a rare entity affecting mainly young people and generally manifesting with nodal involvements. The lack of MYC translocation is the hallmark of BLL-11q while the morphological features of BLL-11q resemble those of classical Burkitt lymphoma (BL). Therefore, BLL-11q is usually treated according to the recommendations for classical BL. However, there is no standard of care in patients with BLL-11q.

This research presents a 19-year-old man with the initial diagnosis of appendicitis. Microscopic examination of resected tissue, supported by immunohistochemistry and fluorescence in situ hybridization finally confirmed the diagnosis of BLL-11q. The patient was treated with R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternately with rituximab, methotrexate, cytarabine), a protocol dedicated to classical BL. After 3 cycles of that treatment, complete metabolic response was achieved. Due to the prolonged myelosuppression observed after 4 cycles of the immunochemotherapy, the treatment was de-escalated to 2 additional cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone). Post-therapeutic neutropenia grades 3 and 4 without any infections were observed up to six months after the end of treatment. The patient displayed no clinical or laboratory symptoms of the disease during the 18-months follow-up.

Key words: Burkitt-like lymphoma with 11q aberration, symptoms, treatment

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Introduction

Burkitt lymphoma (BL) is a highly aggressive disease that accounts for about 2% of all lymphomas in the whole population. The disease affects mainly children and young adults, and it is often manifested by extranodal location, such as facial bones or abdominal organs. Three variants of BL were distinguished based on the pathophysiology, geographical distribution and clinical manifestation. The endemic variant of BL occurs in Equatorial Africa and Papua, New Guinea and typically affects boys between the ages of 4 and 7 years. The endemic variant is strictly correlated with Epstein-Bárr virus (EBV) infection. In turn, the sporadic variant and human immonodeficency virus (HIV)-associated variant of BL are spread worldwide affecting mainly young adults without being

Address for correspondence: Ryszard Swoboda, Klinika Transplantacji Szpiku i Onkohematologii, Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy, Oddział w Gliwicach, Wybrzeże Armii Krajowej 15, 44–102 Gliwice, Poland, e-mail: ryszard.swoboda@io.gliwice.pl

strictly correlated with EBV infection (EBV positive in 25–40%). The initial diagnosis of BL is made based on microscopic examination which reveals a classic starry-sky appearance of intermediate in size, nonpleomorphic cells with basophilic cytoplasm containing small vacuoles and round nuclei. The proliferation rate is typically almost 100% and the *MYC* translocation, primarily between chromosomes 8 and 14, is characteristic for all variants of BL. However, the *MYC* rearrangement is also detected in other aggressive lymphomas termed "high-grade B-cell lymphoma (HGBCL) with MYC and BCL-2 and/or BCL-6 rearrangement" and "HGBCL, not otherwise specified" [1]. Moreover, RNA sequencing studies have recently shown novel mutations that cooperate with *MYC* rearrangement in BL, such as *TCF3, ID3* or *CCND3* mutations [2, 3]. Another aberration affecting the long arm of chromosome 11 was found in another aggressive lymphoma, resembling morphologically BL, but lacking *MYC* translocation. Therefore, a new provisional entity termed "Burkitt-like lymphoma with 11q aberration" (BLL-11q) was incorporated into the revised World Health Organization (WHO) classification [1]. Because of the similarity of BL and BLL-11q, the common and distinguishing characteristics of these entities were summarized in Table 1.

Given very limited data on the clinical manifestation of BLL-11q as well as diagnostic difficulties and no treatment standards for BLL-11q it was aimed to demonstrate the diagnostic process and effective treatment in a young man with BLL-11q.

Case report

We present a 19-year-old man suffered from abdominal pain in the right lower quadrant since October 2019. No comorbidities were reported. After about three weeks from the beginning of the complaints, the patient was admitted to the hospital. Based on physical examination and the computed tomography scans, appendicitis with localized lymphadenopathy was diagnosed and appendectomy was performed. After surgery, the patient's clinical status has been improving gradually.

Microscopic examination of the resected tissue showed diffuse proliferation of intermediate-sized atypical lymphoid cells with prominent nucleoli in the background of apoptotic debris (Figure 1A). By immunohistochemistry, the high-grade cells were positive for CD20, CD10, BCL-6, CD44, CD56 and negative for ALK1, BCL-2, CD3, CD5, CD21, CD23, CD25, CD30, CD34, CD38, CD43, TdT, cyclin D1 and MUM-1 (Figure 1B–E).

Table 1. Common and distinguishing characteristics of Burkitt lymphoma (BL) and Burkitt-like lymphoma with 11q aberration (BLL-11q)

Parameter	Burkitt lymphoma	Burkitt-like lymphoma with 11q aberration
Common characteristics		
Aggressive lymphoid neoplasm	Yes	
Morphological examination	„Starry-sky" pattern and high proliferative rate	
Immunophenotype	CD10+, BCL-6+, BCL-2(–), and Ki-67 approaching 100%	
Differentiating characteristics		
The most common site of involvement	Ileocecal area and facial bones	Usually lymph nodes
HIV and/or EBV	Positive	Negative
MYC rearrangement	Yes, usually t(8;14)	No
11q aberration	Usually no	Yes (proximal gains or telomeric losses)
1q gains	Yes	No
TCF3/*ID3* mutation	Yes (70% in sporadic and immunodeficiency-related BL and 40% in endemic variant)	No
CCND3 mutation	Yes (about one-third of sporadic variants)	No
Expression of LMO2 protein (a marker of germinal centre origin)	Downregulated	Positive
Karyotype	Less complex	More complex

EBV — Epstein-Bárr virus; HIV — human immunodeficiency virus; LMO2 — LIM domain only 2 (rhombotin-like 1)

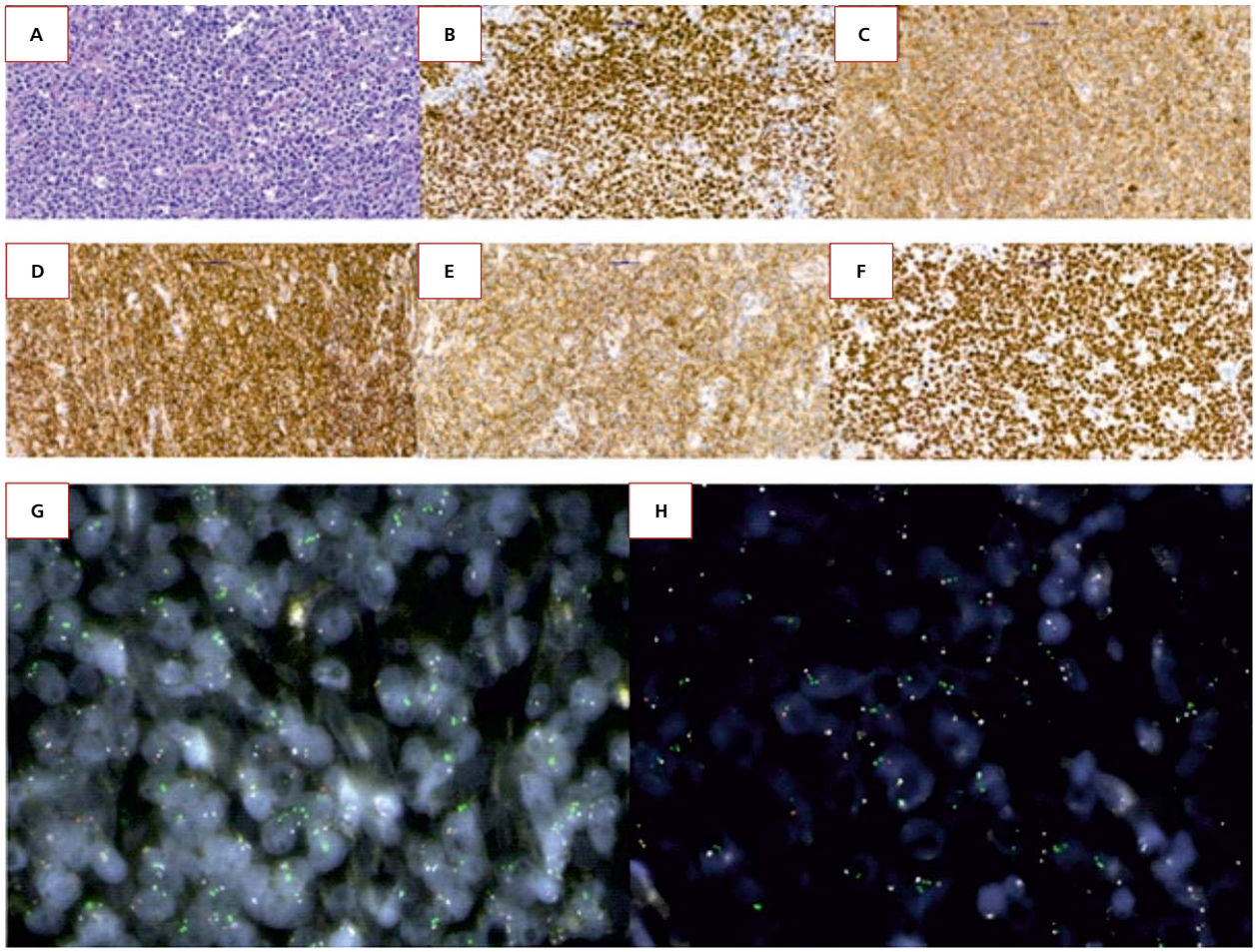

Figure 1. Appendix tissue of 19-year-old male — haematoxylin–eosin (**A**), original magnification 40×. Cells are positive for BCL6 (**B**), CD10 (**C**), CD20 (**D**), CD56 (**E**) and show high proliferative index of Ki-67 > 95% (**F**) (original magnification 40×). Fluorescence *in situ* hybridization (FISH) testing (**G, H**) (original magnification 100×) show rearrangements — nuclei with amplification of 11q23.3 (green) and deletion of 11q24.3 (orange), 11q11 — α satellite centromeric region of 11 chromosome (aqua)

Partial, heterogeneous, in < 40% of cells protein expression of C-myc made this result unreliable. Ki-67 highlighted a high proliferative index > 95% (Figure 1F). Fluorescence *in situ* hybridization (FISH) testing with break-apart probes specific for rearrangements of the *MYC* gene did not show any abnormal rearrangements. Qualitative detection of 11q alterations by FISH finally confirmed the diagnosis of BLL-11q (Figure 1G–H).

On the first admission to the clinic in January 2020, the patient felt no pain but reported weight loss (10 kg within three months) and night sweats. The positron emission tomography (PET) scans revealed very extensive pathological infiltration at the level of the mesogastrium and lower abdomen from the exit of the superior mesenteric artery to the pelvis, located predominantly on the left side, with suspected infiltration of the inferior vena cava, displacing the intestinal loops and emphasizing the abdominal wall, especially at the level of the right hypogastrium. It was decided to start chemotherapy according to the R-hyper--CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternately with rituximab, methotrexate, cytarabine) protocol [4]. In the interim PET after a total of 3 cycles of R-hyper-CVAD given every 3 weeks, complete metabolic response (CMR) was achieved. This intensive treatment was continued for a total of 4 cycles. Due to the prolonged regeneration of haematopoiesis after 4 cycles of that therapy, it was stopped and the patient was given 2 cycles of the R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone) regimen,

which is a standard of care for patients with diffuse large B-cell lymphoma. In PET scans after 3 and 12 months after the end of treatment CMR was maintained. However, up to six months after the end of treatment, post-therapeutic neutropenia grades 3 and 4 according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) without any infections was observed [5]. The patient displays no clinical or laboratory symptoms of the disease in 18 months of follow-up.

Discussion

This case report showed the clinical manifestation as well as the diagnostic process of BLL-11q resembling appendicitis in a young man. BLL-11q was first incorporated in the revised 4th edition of WHO classification in 2017 as a new provisional entity characterized by 11q aberration with morphological and immunohistochemical similarity to BL and HGBCL [1]. To distinguish these entities, detailed molecular and cytogenetic diagnostics are required, which makes the diagnosis of BLL-11q very challenging [6]. Moreover, the effective treatment of the patient with well-tolerated, temporary side effects was demonstrated. Given the lack of standards for treatment in this entity, this case report may be helpful for physicians treating patients with BLL-11q.

The hallmarks of BLL-11q comprise the lack of *MYC* rearrangements, 11q aberrations as well as morphological and immunophenotypic similarity to BL. Morphologically, BLL-11q displays as a diffuse lymphoid infiltration of medium-sized cells with round nuclei and a few small nucleoli creating a classical starry-sky pattern typical of BL in many cases. BLL-11q is also characterized by a very high Ki-67 and the signature of germinal centre B-cell (GCB). However, Rymkiewicz et al. showed subtle morphological differences in 6 out of 11 studied cases demonstrating a reduced number of macrophages and apoptotic bodies in relation to classical BL [6].

BLL-11q also resembles BL in relation to the gene-expression profile, however, the karyotype in BLL-11q was shown to be more complex. The 11q aberration mostly presents as proximal gains or telomeric losses in this chromosome. The duplication of 11q is the most common aberration leading to the gain of different sizes of a duplicated region [7]. Although the 11q aberration is a hallmark of BLL-11q which lacks *MYC* rearrangements, this aberration was also detected in retrospective analyses of several MYC-positive BL and HGBCLs [8, 9]. Therefore, it remains unclear if 11q is a primary or a secondary genetic change in those lymphomas. However, BLL-11q is believed to be genetically unrelated to BL [10].

As far as a clinical manifestation of BLL-11q is concerned, limited information is available from a few case reports. In general, BLL-11q is diagnosed in children and young adults and localized lymphadenopathy, especially in the head and neck region, is the most common clinical manifestation [10, 11]. Among 11 cases presented by Gonzales-Farre et al. [10], all patients were younger than 40 years and only two patients demonstrated extranodal manifestation, including appendix and omentum. However, in a case report by Moshref Razavi et al. [12], BLL-11q was diagnosed in an 82-year-old man based on bone marrow aspirate. Moreover, the BLL-11q was also detected in three out of seven patients with a primary morphological diagnosis of BL after organ solid transplantation indicating the significant role of 11q aberration in the development of post-transplant lymphoproliferative disorders [13].

The data on the treatment methods for patients with BLL-11q is much more limited. Due to many features of BLL-11q resembling those of BL, most patients with a final diagnosis of BLL-11q were initially diagnosed and thereby also treated with regimens dedicated to BL, such as R-CODOX-M/R-IVAC (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with fractionated ifosfamide, etoposide and high-dose cytarabine, along with intrathecal methotrexate and cytarabine) or GMALL-B-ALL/NHL2002 protocol (rituximab, fractionated cyclophosphamide or ifosfamide, vincristine, methotrexate, cytarabine, teniposide, and prednisone or doxorubicin). These regimens resulted in 5-year overall survival at 80% [6]. However, the detailed data on the number of cycles of individual regimens as well as adverse effects of the treatment is missing. On the other hand, Wang et al. [11] showed a 34-month remission after a cycle of R-CTOEP (rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisone) in patients with acquired immunodeficiency syndrome (AIDS). Given this example, it remains unclear, how intensively patients with BLL-11q should be treated. In this case report the combined treatment protocol for BLL-11q is shown which is based on 4 cycles of R-hyper-CVAD, originally dedicated for patients with classical BL, followed by 2 cycles of R-CHOP. Originally, R-hyper-CVAD should be used every 14–21 days up to a total of 8 cycles (without

rituximab in the last four cycles). Furthermore, each cycle includes intrathecal co-administration of methotrexate and cytarabine [4]. In this case, however, the prolonged dysfunction of haematopoiesis observed after four cycles of R-hyper-CVAD was the reason for changing the treatment to the less intensive regimen R-CHOP. The de-escalation of the treatment maintained complete metabolic response and it was likely to prevent further bone marrow suppression. Therefore, this de-escalated treatment protocol is suggested as one of the effective and safe methods to cure patients with BLL-11q.

Conclusions

Clinical symptoms of appendicitis may be the first manifestation of BLL-11q. Both the diagnostic and treatment processes of BLL-11q are very challenging. The de-escalated treatment comprised 4 cycles of R-hyper-CVAD followed by 2 cycles of R-CHOP proved to be very effective and well-tolerated.

Conflict of interest

None.

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