Lymphoma and Chronic Lymphocytic Leukemias

CASE REPORT

Adult Atypical Sporadic Burkitt Lymphoma Successfully Treated with Bendamustine and Rituximab

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Abstract: Sporadic Burkitt lymphoma (BL) accounts for 1% to 2% of lymphomas in adults. The abdomen is the most common site of involvement. The 2008 *World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues* introduced a new category of high-grade B-cell lymphomas: an entity with overlapping features of both diffuse large B-cell lymphoma and Burkitt lymphoma (DLBCL/BL). These lymphomas reportedly have poor overall survival rates. We present a case of an elderly adult atypical sporadic BL with jaw and bone marrow involvement. The tumor had the typical characteristic of BL including atypical monotonous lymphoid infiltrate with a starry-sky appearance and a high Ki67 proliferate index of 95%. MYC/IgH rearrangement was seen in 93.5% of the cells with 92% of cells also positive for IgH/Bcl-2, a feature of double-hit lymphoma. This atypical case of adult sporadic BL had features as classified of DLBCL/BL. Though high intensity regimen is used in BL and atypical BL, elderly patients tend to not tolerate these regimens well. Our patient was treated with bendamustine and bituximab given herelderly age and poor cardiac status. The patient responded well to chemotherapy and remains in complete remission two years after diagnosis up to the date of this report. The atypical presentation and excellent response to bendamustine plus rituximab has not been previously reported.

Keywords: burkitt lymphoma, double-hit lymphoma, bendamustine

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Introduction

Burkitt lymphoma (BL)/leukemia is a rare, aggressive B-cell neoplasm with typical morphologic appearance. It is characterized by rapid proliferation of mature B cells (Ki67/MIB-1 staining ≥ 99%) and overexpression of *c*-Myc (most commonly from the translocation t [8;14] and less frequently from t [2;8] and t [8;22]). Three clinical variants of BL are described: endemic, sporadic, and immunodeficiency-associated types. These account for 1% to 2% of lymphomas in adults and 40% of lymphomas in children in the United States and Western Europe.[1] Endemic Burkitt lymphoma refers to cases occurring in African children, usually 4 to 7 years old, with a male to female ratio of 2:1. These cases usually involve the bones of the jaw and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast, central nervous system (CNS), and other extra nodal sites.[2] Immunodeficiency-associated BL, occurring mainly in patients infected with HIV, is also seen in allograft recipients[3,4] and individuals with congenital immunodeficiency. Sporadic BL is an uncommon form of non-Hodgkin's lymphoma in adults with an incidence of approximately 1100 patients per year in the United States as per the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) registries (1992–2001). Its incidence rates are significantly higher among males in the pediatric and adult population as compared with geriatric patients.[5] Neoplastic cells are EBV positive in 15% to 30% of cases or fewer in some series.[6] Jaw involvement is relatively rare (about 7% of patients).[7]

The World Health Organization (WHO) classification (2008) describes a variant of B-cell lymphoma as unclassifiable, which has intermediate features of both diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL).[6–8] We report a case of atypical BL with characteristic BL morphology, MYC/IgH translocation, EBV negative with jaw involvement, poor bone marrow cytogenetics, and absence of BCL-2 protein but positive for MYC/BCL-2 rearrangement (a characteristic feature of double-hit lymphoma) likely belonging to the category of B cell lymphoma variant, unclassifiable (DLBCL/BL). These lymphomas reportedly have poor overall survival rates even when treated with intense regimens.[9,10] However, this case had a favorable response to initial treatment with bendamustine and rituximab, which has not been previously reported.

Case Report

Patient is an 85-year-old female with a medical history of congestive heart failure (systolic dysfunction with ejection fraction of 35%), atherosclerotic heart disease, coronary artery stent placement in 2009, atrial fibrillation, hypertension, and chronic kidney disease (stage 4) secondary to long-standing hypertension. In June 2010, she developed swelling of the submandibular area, which gradually increased in size during the next 3 to 4 weeks (Fig. 1). A computer tomography (CT) scan of the neck showed a 5.6 × 3.7 × 5.2 cm soft-tissue mass located inferior to the mylohyoid muscle sling and extensive bilateral

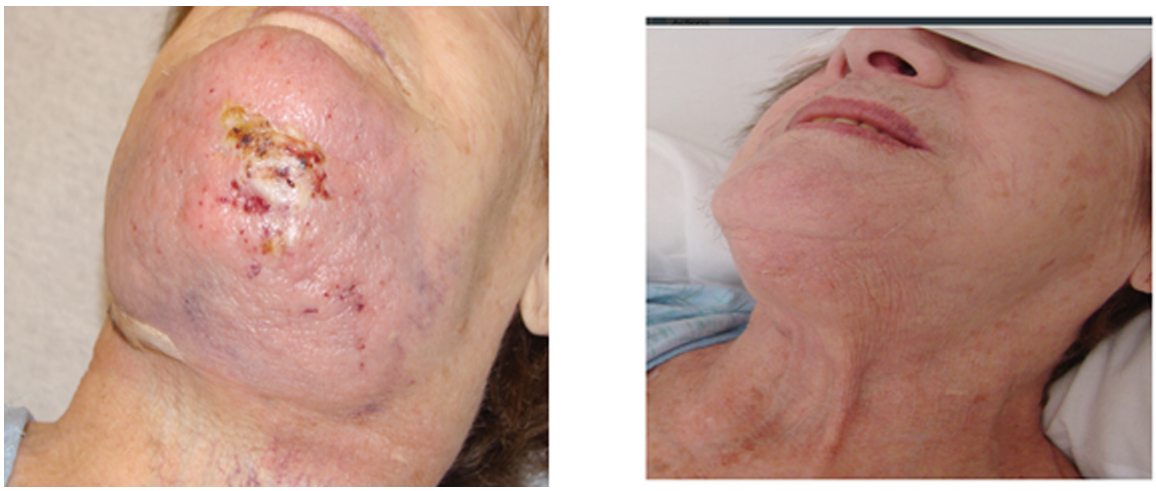

Figure 1. Patient presented as a huge submandibular mass with inflammation and purulent ulceration (left). Complete resolution of the submandibular mass is seen post chemotherapy (right).

cervical lymphadenopathy measuring 4–5 cm (Fig. 2). Surgical pathology of the submandibular mass showed fragments of tissue with atypical lymphoid infiltrates consisting of relatively monotonous, medium-sized lymphocytes with finely clumped chromatin, medium-sized nucleoli, and basophilic cytoplasm. Low-powered microscopic view showed a starry-sky appearance with atypical cells demonstrating frequent mitotic figures and apoptosis characteristic of BL morphology (Figs. 3 and 4). Immunohistochemistry (IHC) stained positive for CD20, Bcl-6, CD10, CD79a, and CD45 and negative for ALK1, Bcl-1, Bcl-2, CD15, CD23, CD30, CD3, CD5, and MUM1 (Table 1). FISH study for EBV was negative. Ki67 proliferate index was highly positive in 95% of the atypical cells. Of the cells, 93.5% were positive for MYC/IgH rearrangement with 92% of the cells also positive for IgH/Bcl-2 translocation (t [14;18]) but absent for Bcl-2 protein expression, findings suggestive of double-hit lymphoma. The bone marrow showed atypical monotonous lymphoid infiltrate composed of medium-sized lymphocytes with finely clumped chromatin, medium-sized nucleoli, and basophilic cytoplasm. The IHC was positive for CD20, CD10, BCL-6 and negative for BCL-2, CD3. Ki67 indicated a high proliferate index with cells negative for TdT. Flow cytometry analysis performed on the biopsy showed B-cell population positive for CD19, CD20, CD22, and CD10 with loss of surface immunoglobulin expression. The typical morphological features of monotonous, medium-sized, mononuclear cells producing a starry-sky appearance, TdT^{-}ve, $CD10^{+}$ve, $BCL\text{-}6^{+}$ve, high Ki67 of more than 95% of atypical cells, t(8;14) and t(14;18) favored the diagnosis of Burkitt lymphoma histologically. The bone marrow cytogenetics were noted to be complex: (47,XX+X, t(8;14)(q24;14)(q24;q32), t(14;18)(q32;q31), add(17)(q25)(cp17)/47, idem, add(17)(q25)x2[cp4] with the absence of BCL-2 protein expression. Cerebrospinal fluid (CSF) was also analyzed to rule out leptomeningeal involvement of lymphoma and was found to be negative. After careful review of the patient's condition (an elderly patient with multiple cardiac-related complications), she was found to be not an ideal candidate for high-dose chemotherapy traditionally used to treat Burkitt lymphoma. A more tolerable regimen of bendamustine (80 mg/m^2 day 1 and 2) and rituximab (375 mg/m^2) q28 days was started in July of 2010. Despite prophylactic allopurinol and hydration plus alkalization of urine, the patient developed acute renal failure secondary to tumor lysis syndrome. She was treated with rasburicase along with active intravenous hydration. Her acute renal failure resolved without the need for dialysis. Magnetic resonance imaging (MRI) of the brain and CSF flow cytometry was negative for any evidence of lymphomatous involvement. Prophylactic chemotherapy with intrathecal methotrexate was given via Omaya reservoir. The patient received two cycles of systemic chemotherapy. Complications included severe neutropenia and related infections. However, she responded very well to her therapy with complete resolution of her enlarged lymph nodes as well as her thickened jaw (Figs. 1 and 3). Her last positron

Table 1. Immunochemical studies of the submandibular mass and bone marrow.

Submandibular Mass		Bone Marrow	
Positive	**Negative**	**Positive**	**Negative**
CD20	CD15	CD20	CD3
CD10	CD23	CD10	BCL-2
CD79a	CD30	BCL-6	TdT
CD45	CD5		
BCL-6	CD3		
	BCL-1	**FLOW CYTOMETRY**	
	BCL-2	*B cell population with CD19, CD20, CD22 and CD10 with loss of sIg*	
	ALK-1		
	MUM-1		

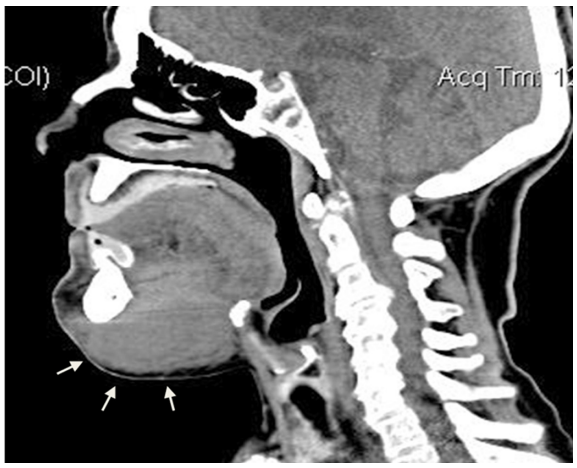

Figure 2. CT scan of the neck, sagittal view, showing 5.6 × 3.7 × 5.2 cm soft tissue mass located inferior to the mylohyoid muscle sling.

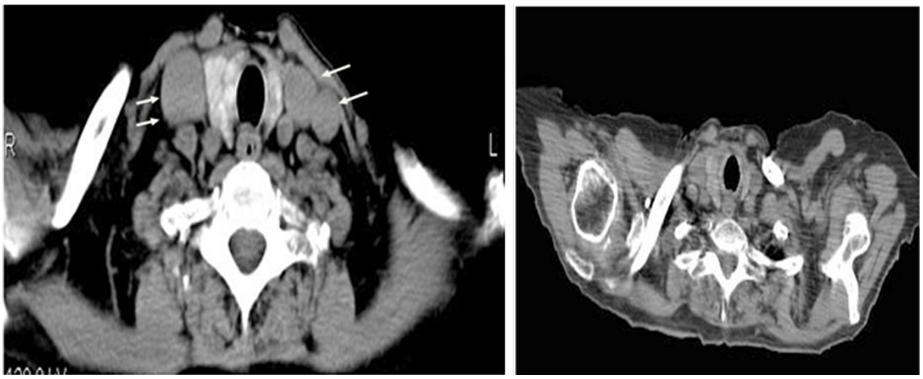

Figure 3. Pre and post-treatment, noncontrast CT scan demonstrating complete resolution of the 5- to 6-cm submental soft tissue mass.

emission tomography (PET) scan showed no evidence of any residual malignancy. Given her advanced age and possible strenuous side effects, patient decided against any further chemotherapy. However, she has remained in complete remission up to the date of this present report.

Discussion

The 2008 *World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues* introduced two new categories of high-grade B-cell lymphomas, entities in which features of DLBCL overlap with BL or classical Hodgkin's lymphoma (HL). The DLBCL/BL category encompasses cases with intermediate features between BL and DLBCL.[8] Many of the cases in the DLBCL/BL category contain MYC translocation and either BCL-2 or BCL6 (so-called double-hit lymphomas), which have very aggressive clinical behavior.[11] Recognized prognostic factors in BL are old age, elevated lactate dehydrogenase, poor performance status, and advanced-stage disease. These are used in some protocols to distinguish between low-risk and high-risk disease.[12,13] B-cell lymphomas with concurrent IgH/Bcl-2 and MYC rearrangements, also known as DHL, are rare neoplasms characterized by highly aggressive clinical behavior, complex karyotypes, and a spectrum of pathologic features overlapping between BL, DLBCL, and B-lymphoblastic lymphoma/leukemia (B-LBL). The clinical and pathological spectrum of this rare entity, including comparison to other high-grade B-cell neoplasms, has not been well defined.[14]

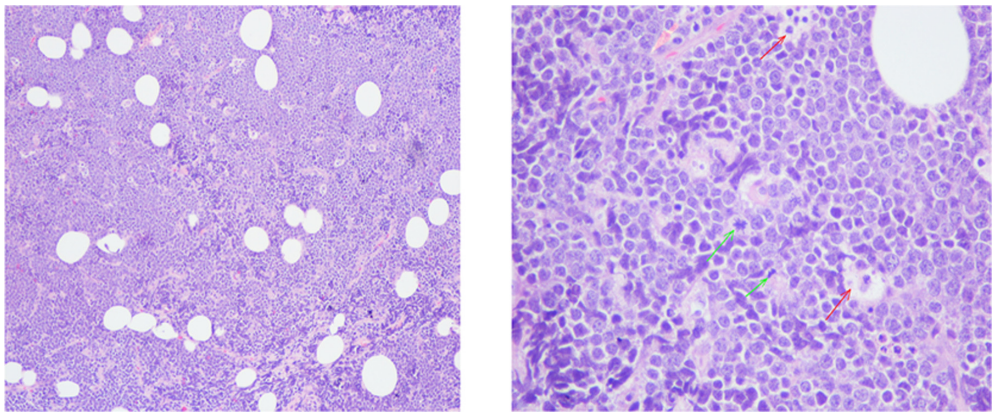

Figure 4. Low power view of lymph node biopsy showing marked atypical lymphoid cell infiltrates and starry sky appearance.
Notes: High power view of lymph node biopsy showing atypical lymphoid infiltrate consisting of relatively monotonous, medium-sized lymphocytes with finely clumped chromatin, medium-sized nucleoli, and basophilic cytoplasm. The atypical cells show frequent mitotic figures and apoptosis. The tumor cells are positive for CD20, Bcl-6, CD10, CD79a, and CD45 and negative for CD3, CD5, ALK-1, Bcl-1, Bcl-2, CD15, CD23, CD30, and MUM-1. EBV in situ hybridization is negative. Ki-67 is positive in more than 95% of the atypical cells. 93.5% of the cells are positive for MYC/IgH rearrangement, and 92% cells are positive for IgH/Bcl-2 translocation and negative for IgH/Bcl-6 translocation. (Not shown are the immunochemical and FISH staining.)

DHL has an aggressive clinical presentation and a poor prognosis with a median overall survival of 0.2 to 1.5 years with current available therapies.[15,16]

In our case, the morphology of tumor showed atypical lymphoid infiltrate consisting of relatively monotonous, medium-sized lymphocytes with finely clumped chromatin, along with medium-sized nucleoli and basophilic cytoplasm with starry sky appearance. The absence of Bcl-2 by immunochemical stain, involvement of the jaw, and MYC/IgH rearrangement positivity in 93.5% of cells favored the diagnosis of BL. However, IgH/Bcl-2 translocation positivity was also seen in 92% of cells, which suggest a diagnosis of DHL. Based on these findings, this was likely a case of atypical adult sporadic Burkitt lymphoma, classified as intermediate between DLBCL and BL.[8] Dr. E. Jaffe, at the National Institutes of Health, was consulted and also favored the diagnosis of atypical BL. High-intensity regimens used in BL are also considered as treatment options for atypical Burkitt lymphoma/DHL, even though studies have not shown a clear benefit in the use of high-intensity regimens in DHL patients.[14] An extensive literature search did not yield any substantial information on bendamustine and rituximab used as initial management of atypical Burkitt lymphoma.

Despite being positive for IgH/Bcl-2 translocation, our patient lacked the expression of Bcl-2 protein. Bcl-2 family proteins regulate all major types of cell death, including apoptosis, necrosis, and autophagy. Its expression is considered as a poor prognostic factor. Overexpression of Bcl-2 protein has also been shown to confer resistance to chemotherapy. Rituximab in addition to CHOP has been shown to overcome Bcl-2 resistance in elderly patients with DLBCL.[17,18] Lack of Bcl-2 protein expression in our patient could partially explain her unexpected complete response.

The outcome of adult patients with BL, particularly those over 40, is inferior to the outcome of younger patients. Authors of 12 large treatment series (10 prospective, 2 retrospective) provided detailed outcome information about patients over the age of 40 enrolled in their clinical trials. The pooled analysis included 470 adult patients with BL; 183 of the patients were 40 years or older (39%). Patients aged 40 and above had significant inferior outcomes in 10 of the 12 series. The median overall survival (OS) at 2 years for patients treated with short-duration therapy was 71%, and for patients greater than age 40 OS at 2 years was 39%. The OS at 2 years for all patients treated with ALL-like therapy was 51%, and for patients older than age 40 years, 40%.[19] Very few patients aged 60 and above with BL have been included in prospective therapeutic trials. According to data from SEER, up to 30% of BL diagnoses in the United States include this group of patients. Although the relatively small number of patients older than 60 treated with the HyperCVAD-rituximab regimen had favorable outcomes,[20] studies of HyperCVAD in other histologies have demonstrated the inability of the majority of elderly patients to tolerate this regimen.[21] Older patients may not be able to tolerate high doses of methotrexate and cytarabine included in many short-duration protocols and also may not be candidates for autologous stem cell transplantation.

For elderly patients not suitable for these intensive therapies, new therapeutic options are clearly required. Bendamustine with rituximab, drugs that are tolerated better by the elderly population, could be one such alternative. Bendamustine hydrochloride is an alkylating agent approved by the FDA for treating patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that progresses during or within 6 months of treatment with rituximab or a rituximab-containing regimen. It is also approved for treatment of chronic lymphocytic leukemia (CLL). Bendamustine as a single agent is effective against aggressive lymphoma, even in cases of refractory disease. In a phase II study of 21 patients reported by Weidmann et al[22] with relapsed or refractory high-grade NHLs, 18 were evaluated for response and toxicity with 10 of these refractory to previous chemotherapy. Three patients achieved a complete response (at 6, 8, and 22 months) and five achieved partial response (three at 2 months, one at 3 months, and one at 10 months); the total response rate of evaluated patients was 44% (8 out of 18, 38% of all patients).[22] Subsequently in 2011, Weidman et al also reported a phase II study of bendamustine and rituximab as first-line treatment in elderly patients (≥80 years) with aggressive B-cell lymphomas who were not eligible for R-CHOP or who did not agree to aggressive treatment.[23] Thirteen patients were assessed for response. Seven patients (54%) had a complete response, two (15%) had a partial response, and four (31%) had progressive disease. The median overall survival was 7.7 months, and the median

progression-free survival was 7.7 months. However, six patients (43%) were alive without disease at 20 to 72 months after the start of treatment.[23] In both reports, only one case was mentioned as unclassified aggressive B-cell lymphoma. Whether our case belongs to the same category is not clear. Regardless, her strikingly favorable response to bendamustine and rituximab is noteworthy here.

Despite having multiple poor prognostic factors such as old age and complex bone marrow cytogenetics, our patient had a complete response to this regimen. A randomized clinical trial of this regimen to treat aggressive lymphoma such as atypical Burkitt lymphoma or unclassifiable lymphoma between DLBCL and BL may be necessary in future studies.

Author Contributions

VPK, First Author, collected the patient information, reviewed the literature, and drafted the manuscript. JCW, Corresponding Author, designed the treatment protocol, and attended the patient; assisted and mentored in the writing the manuscript. AS, assisted in collecting the relevant clinical data and wrote the revised manuscript. AG, Interpreted the radiology findings and collected the radiology data. KK, Collected all the pathology data and interpreted all pathological data. AK, assisted in collecting the data, took care of the patient and helped in writing the manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

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