CASE REPORT

“Double hit” follicular lymphoma with low proliferation index: A unique case and literature review

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Abstract: “Double hit” lymphomas (DHLs) are aggressive B-cell lymphomas with concurrent c-MYC and BCL2 and/or BCL6 gene rearrangements. DHLs are usually classified morphologically as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, and less commonly as DLBCL. Follicular lymphoma (FL) is characterized genetically by the presence of IGH-BCL2 rearrangement. A subset of DHLs arises from FL by the acquisition of c-MYC gene rearrangement during disease progression, but FL with concurrent IGH-BCL2 and c-MYC gene rearrangements initial is rarely reported. The few reported cases had different clinical courses, including some with indolent disease. We report a case of “double hit” low-grade FL with both c-MYC and BCL2 gene rearrangements but low proliferation rate. Unlike the usual DHLs with aggressive clinical course, our patient showed at least partial response to intense chemotherapy. Review of the literature shows a few similar cases with variable clinical course, including a few indolent cases. These patients appear to respond better with more intense chemotherapy for DHL.

Keywords: “double hit”; follicular lymphoma; c-MYC; BCL2

Introduction

“Double hit” lymphoma (DHL) is defined as large B-cell lymphoma with MYC and BCL2 and/or BCL6 gene rearrangements identified cytogenetically[1]. Most DHLs show morphologic features of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. The lymphoma cells in these cases infiltrate the tissue diffusely and are mostly medium-sized lymphoid cells with brisk mitotic figures and prominent apoptotic bodies, some with at least focal “starry sky” pattern of scattered tingible body macrophages. A minority of cases of DHL is morphologically indistinguishable from typical DLBCL, not otherwise specified, with sheets of centroblasts and/or immunoblasts. DHLs are highly aggressive with rapid progressive clinical course, and usually show poor response to standard chemotherapy used for DLBCL[2-7]. Therefore, clinically it is important to diagnose DHL accurately and differentiate it from DLBCL for proper treatment and prognosis. DHLs are diagnosed by cytogenetic methods, most commonly by fluorescence in situ hybridization (FISH) with probes targeting MYC, BCL2 or IGH-BCL2, and BCL6 gene loci[8]. Other than aggressive large B-cell lymphomas, concurrent MYC and BCL2 gene rearrangements are not seen in other types of lymphomas, except in some rare cases of FL and B lymphoblastic lymphoma[3,9]. A common feature of all DHLs is the rapid proliferation rate of lymphoma cells as demonstrated by immunohistochemical stain for Ki-67. Here, we report a rare case of low-grade FL with both MYC and BCL2 gene rearrangements, but without the high proliferation index typically seen in DHLs.
Case report

Clinical presentation

The patient was a 63-year-old female with past medical history of atrial flutter, line-associated deep vein thrombosis, hypothyroidism, migraine headache, fibromyalgia, and renal insufficiency. A routine mammogram revealed increasing bilateral axillary lymphadenopathy in April of 2011, and a lymph node core biopsy showed grade 1 FL. The lymphoma cells were positive for CD20, BCL6, and BCL2; negative for CD5 and CD10; and showed low proliferation rate by Ki-67 (approximately 30%). The follicular lymphoma international prognostic index (FLIPI) score was 0 at the time. She was closely observed with yearly computed tomography (CT) scans from 2011 to 2015, which showed overall slow and gradual progression of axillary, neck, supraclavicular, and abdominal lymphadenopathy. However, the patient remained asymptomatic and treatment was deferred. On September 11, 2015, her serum lactate dehydrogenase (LDH), Beta2-Microglobulin (B2M), and liver enzymes were noted to be elevated; so, an abdominal ultrasound was performed, which showed hepatomegaly and “mass” adjacent to pancreatic head. In January 2016, she had increasing fatigue as well as increasing palpable left axillary lymphadenopathy. A positron emission tomography (PET) scan on January 18, 2016, showed extensive hypermetabolic lymphadenopathy in axilla (3 cm, standardized uptake value (SUV) 15.95), near pancreatic head (2.5 cm, SUV 14.39), retroperitoneum (4.5 cm, SUV 12), pelvis (4.4 cm, SUV 13.74), neck (1.4 cm, SUV 13.43), supraclavicular areas (1.5 cm, SUV 10.45), mediastinum (3.3 cm, SUV 11.68), periaortic (4.5 cm, SUV 12.8), mesentery, and groin. It also showed hepatosplenomegaly and increased activity in bone marrow. She was noted to have pancytopenia: white blood cells (WBC) was 4.6, with absolute neutrophil count (ANC) of 1.4, hemoglobin 9.1, and platelets 94,000. A left axillary lymph node core biopsy showed low-grade (grade 1–2) FL but with rearrangements in MYC and BCL2 as noted by FISH study. In mid-February of 2016, she began to experience night sweats and worsening fatigue. The FLIPI score was 4. She subsequently was started on chemotherapy with full doses of EPOCH-R (etoposide phosphate, prednisone, oncovin, cyclophosphamide doxorubicin hydrochloride and rituximab) on March 28, 2016. She tolerated the chemotherapy well and noticed regression of neck and axillary lymphadenopathy. She was discharged from the hospital after completing 3 cycles of chemotherapy on May 22, 2016. The patient remains alive with the disease at nine months following the most recent diagnosis. She will complete cycle 4 of chemotherapy and will be evaluated for autologous hematopoietic stem cell transplant.

Pathologic findings

The recent left axillary lymph node needle core biopsy showed vaguely follicular lymphoid infiltrate composed of multiple well-separated vague lymphoid follicles (Figure 1A). There was a predominance of small lymphoid cells with mildly irregular nuclei, fine blastoid chromatin, and inconspicuous-to-distinct nucleoli in the follicles (Figure 1B). The size of these atypical blastoid lymphoid cells was approximately 1.5 times of that of the admixed background small mature lymphocytes. Centroblasts were rarely seen (<15 cells/high power field). These follicles varied in size and focally large lymphoid nodules composed nearly entirely of these blastoid lymphoid cells were present. The interfollicular areas also showed many similar blastoid lymphoid cells admixed with large numbers of background small mature lymphocytes. Immunohistochemical stains showed sheets of CD20 positive B-cells (Figure 1C). BCL6 highlighted the lymphoid follicles, which were variable in size from small to large, and the interfollicular B-cells were mostly negative for BCL6 (Figure 1D). The B-cells were negative for CD10, CD5, CD23, and TdT, and positive for BCL2 (Figure 1E) and MYC (approximately 50% positive, Figure 1G). Of note, both the lymphoid follicles, as well as the interfollicular B-cells, were positive for BCL2 and MYC. CD21 highlighted the follicular dendritic cell meshworks (FDC) of the follicles, and the FDC meshworks were nearly evenly distributed (Figure 1F). Ki-67 showed low proliferation rate (approximately 10%–20%, Figure 1H). Corresponding flow cytometry showed a kappa-restricted monoclonal population of B-cells with dim expression of CD19, dim CD20, and negative CD5, CD10, CD23, CD25, CD103, and FMC-7. FISH studies were positive for t(14;18)/IgH-BCL2 translocation (observed in 62% of the analyzed nuclei), c-MYC gene rearrangement (observed in 65.5% of the analyzed nuclei), and trisomy 18 (observed in 63.5% of the analyzed nuclei).
Discussion

The histologic and phenotypic findings of the recent left axillary lymph node biopsy were consistent with low grade FL, based on current World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues\(^1\). The atypical lymphoid follicles were composed of small blastoid lymphoid cells, which are similar to those seen in low-grade FL with high proliferation index\(^{10}\). However, the lymphoma cells in this case demonstrated low proliferation rate with only 10%–20% positive cells for Ki-67. As the follicles were almost evenly distributed without nodular or mass forming lymphoma cells disrupting the underlying follicular structure, there was no morphologic evidence of DLBCL. Given the presence of \(IgH-BCL2\) translocation, the \(c-MYC\) gene rearrangement identified
by FISH study, and the positive BCL2 and MYC by immunohistochemical stains, this case was best classified as a “double hit” low grade FL.

The patient had a history of low-grade FL five years ago. While the original diagnostic tissue was not available for review, the reported phenotype of lymphoma cells was similar to that of the present biopsy. In both biopsies, the lymphoma cells were positive for BCL6 and BCL2, and negative for CD10. Based on the expression of BCL2 and the presence of IgH-BCL2 translocation, it was clearly revealed that the follicular lymphoma had t(14;18)(q32;q21) IGH-BCL2 fusion initially. As immunohistochemical stains for MYC and FISH studies were not performed in the first biopsy, it was unclear if the original low grade FL already had c-MYC gene rearrangement. As traditional karyotyping studies were not routinely performed clinically in surgical specimens, we cannot postulate if the c-MYC gene rearrangement was a primary or secondary cytogenetic change in this case.

The t(14;18)(q32;q21) IGH-BCL2 fusion is the hallmark cytogenetic change in most cases of FL. The gene fusion results in overexpression of BCL2 protein, with subsequent suppression of apoptosis and survival of lymphoma cells. The c-MYC gene on chromosome 8q24 encodes MYC protein, which is a global transcriptional factor regulating many cell functions including cell proliferation, survival, cellular metabolism, and biosynthesis. c-MYC gene rearrangement as a result of translocation with immunoglobulin gene loci is the genetic hallmark of Burkitt lymphoma, in which the c-MYC gene rearrangement is the primary event in a simple karyotype. c-MYC gene rearrangement also occurs as a secondary event during the progression of FL. In these cases, the acquisition of c-MYC gene rearrangement is in the context of complex karyotype and is accompanied by histologic transformation to aggressive B-cell lymphoma (B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma or DLBCL) and rarely blastoid transformation of FL/B-lymphoblastic lymphoma[1,11]. Therefore, DHL is defined cytogenetically by the presence of both BCL2 and c-MYC gene rearrangements that are composed of both de novo and secondary lymphomas, respectively. Consistent with the pivotal role of MYC protein in cell proliferation and metabolism, DHL usually shows a very high proliferation rate in the lymphoma cells. Probably due to the proliferation and survival advantages conveyed by both MYC and BCL2 overexpression, patients with DHL typically have a very aggressive clinical course and poor prognosis.

Our case did not show the aggressive features typically associated with DHL. Despite the blastoid cytological features of the lymphoma cells, it maintained the follicular structure of DL and showed low proliferation rate as determined by Ki-67 immunostain. Of note, the original FL showed approximately 30% Ki-67-positive cells, and our current biopsy showed approximately 10%–20% Ki-67-positive cells. The difference in the proliferation rates was not clinically significant and inter-observer discrepancy could not be excluded. The patient showed at least partial response to chemotherapy. There were only a few cases of FL with concurrent BCL2 and MYC gene rearrangements in the literature[5,12-16]. Interestingly, most of these were low-grade FL. While some of these patients with low-grade FL were dead within two years of diagnosis[13-15], the two cases reported by Christie et al.[12] showed indolent clinical course, as typically seen in low-grade FL[12]. The different clinical course and prognosis did not seem to correlate with cytogenetic findings, as all three cases reported by Christie et al.[12] had complex karyotypes but yet two cases were clinically indolent and the third patient died 49 months later from high-grade transformation of FL. The proliferation rate by Ki-67 was not reported in many of these cases. However, one of the reported cases showed low proliferation index by Ki-67 (5%); this patient was treated with rituximab and was in remission after seven months of follow-up[16]. Most recently, Miao et al. described the largest series of “double hit” FL[17]. They showed seven cases of FL with both MYC and BCL2 translocations. Most of the cases were low grade FL with only focal high grade FL or focally high proliferation rate. In this series, most had advanced-stage disease, and patients treated with intense chemotherapy for DHL (EPOCH-R) responded well and with complete remission.

Conclusion

“Double hit” FL is rare and clinically shows variable clinical course. Some of these patients may have an indolent clinical course, while others behave more like typical DHL. Due to the limited number of cases reported so far, reliable pathologic and genetic features to predict the prognosis are lacking. Although patients with
“double hit” FL show good response to the more intense chemotherapy reserved for DHL, these patients should be evaluated individually based on clinical, radiologic, pathologic, and genetic findings for proper treatment.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Reference


