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Double-Hit Lymphoma (MYC and BCL6) with Involvement of Skull and Adnexal Lesions: A Case Report and a Review of the Literature

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 20
Final Diagnosis: High grade B cell lymphoma with MYC and BCL6 translocation
Symptoms: Double vision • nausea • vomiting
Medication: —
Clinical Procedure: CT scans
Specialty: Hematology

Objective: Rare disease

Background: Double-hit lymphomas (DHL) belong to a category of very aggressive lymphomas characterized by MYC translocation and either BCL2, or less commonly, BCL6 translocations. Those with BCL6 translocations have a predilection for rare extranodal sites such as the gastrointestinal tract, nasopharynx, and tonsils. Involvement of the skull and adnexal structures is rare. Here we report a case of a young female with both skull and adnexal involvement.

Case Report: A 20-year-old female who presented with hypercalcemia was found to have adnexal, skull, and jaw masses. Workup revealed a stage IV high grade B-cell lymphoma (HGBL) with MYC and BCL6 rearrangements. She was subsequently treated with R-EPOCH and attained complete remission 9 months after her initial presentation. To the best of our knowledge, our patient represents the first reported case of skull and adnexal involvement in HGBL with MYC and BCL6 rearrangement.

Conclusions: Rare extranodal presentations of HGBL with MYC and BCL6 rearrangement should be considered in the differential diagnosis of masses found in unusual sites such as the skull and adnexa. Due to their aggressive nature, early and prompt recognition of these lymphomas is essential for timely administration of appropriate therapy.

MeSH Keywords: Genes, myc • Lymphoma, B-Cell • Proto-Oncogene Proteins c-bcl-6

Abbreviations: **DHL** – double-hit lymphoma; **HGBL** – high grade b-cell lymphoma; **H&E** – hematoxylin and eosin; **FISH** – fluorescent *in-situ* hybridization; **WHO** – World Health Organization; **LDH** – lactate dehydrogenase; **CNS** – central nervous system; **R-CODOX/MVAC** – chemotherapy regimen consisting of vincristine, doxorubicin, cyclophosphamide, cytarabine, methotrexate, filgrastim; **HyperCVAD** – chemotherapy regimen consisting of cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, mesna, and methotrexate; **R-EPOCH** – chemotherapy regimen consisting of rituximab, etoposide phosphate, prednisone, vincristine, cyclophosphamide and doxorubicin; **DA-EPOCH** – chemotherapy regimen consisting of dose adjusted etoposide phosphate, prednisone, vincristine, cyclophosphamide and doxorubicin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/909400

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Background

High grade B-cell lymphomas (HGBL) are usually characterized by cytogenetic abnormalities involving MYC with BCL2 and/or BCL6 according to the World Health Organization (WHO) 2016 Classification [1,2]. These lymphomas were formerly known as "double-hit lymphomas" (DHL) or "triple-hit" lymphomas. Morphologically, they appear intermediate between diffuse large B-cell lymphomas (DLBCL) and Burkitt lymphoma (BL) [2]. Burkitt lymphoma is characterized by a MYC oncogene translocation to either the IGH locus at 14q32, the IGK locus at 2p12, or the IGL locus at 22q11 [3,4]. DHL is characterized by a MYC locus translocation and an additional translocation, such as BCL2 on chromosome 18 or BCL6 on chromosome 3 [4]. MYC(+)/BCL6(+) lymphomas represent only 8% of double-hit lymphomas compared to MYC(+)/BCL2(+), which account for 62% of the cases [4]. They frequently involve extranodal sites and are clinically aggressive tumors [5]. Identifying constituent cases within this rare category of lymphomas is critical, as treatment regimens are different and outcomes remain poor despite induction chemotherapy [6]. Thus far, there have been only 2 cases reported in the literature of a "double-hit/triple-hit lymphoma" involving the skull (one patient with a MYC/BCL2 translocation, the other patient having a MYC/BCL2/BCL6 translocation) [1,7]. To our knowledge, this is the first case of HGBL with MYC and BCL6 rearrangements involving both the skull and the adnexa.

Case Report

A 20-year-old female presented to the Emergency Department with the chief complaint of nausea and vomiting, loss of sensation on the left side of the face and both sides of tongue, and double vision. These symptoms had started 2 weeks prior to the Emergency Department visit and had progressively become worse. Upon initial evaluation, she was found to have a non-tender palpable mass on the left forehead, lateral rectus palsy on the right side, and fullness in the flanks of the abdomen. A computed tomography (CT) scan of the head revealed 3 skull lesions associated with extension into the epidural space and subcutaneous soft tissue (Figure 1). We could not distinguish whether they were metastatic or inflammatory lesions. The CT of the sinuses revealed areas of bone erosion of the posterior aspect of the right maxillary sinus and in the posterior aspect of the right side of the mandible. Initial laboratory evaluation was significant for elevated LDH (8410 IU/L), hyperuricemia (12.3 mg/dL), and positive EBV VCA IgG and negative IgM. The patient was started on intravenous fluids and one dose of rasburicase was administered. A neurosurgical consultation was obtained, and a left craniotomy was performed. Approximately 3.5×3.5 cm left subcutaneous mass and 8×4 cm fibrous lesion in the left epidural area were resected. Pathology of the specimens revealed high grade CD10 positive B-cell lymphoma (Figure 2). Fluorescent *in-situ* hybridization (FISH) analysis from the skull mass revealed t(8: 14)(C-MYC) (Figure 3) and BCL6(3q27) rearrangement. Subsequently, CT scan of neck/chest/abdomen/pelvis was performed and revealed 9.0×12.0×13.2 cm and 10.7×8.1×5.4 cm soft tissue masses with peripheral follicles in the right and left adnexal areas respectively (Figure 4). It also showed prominence of the

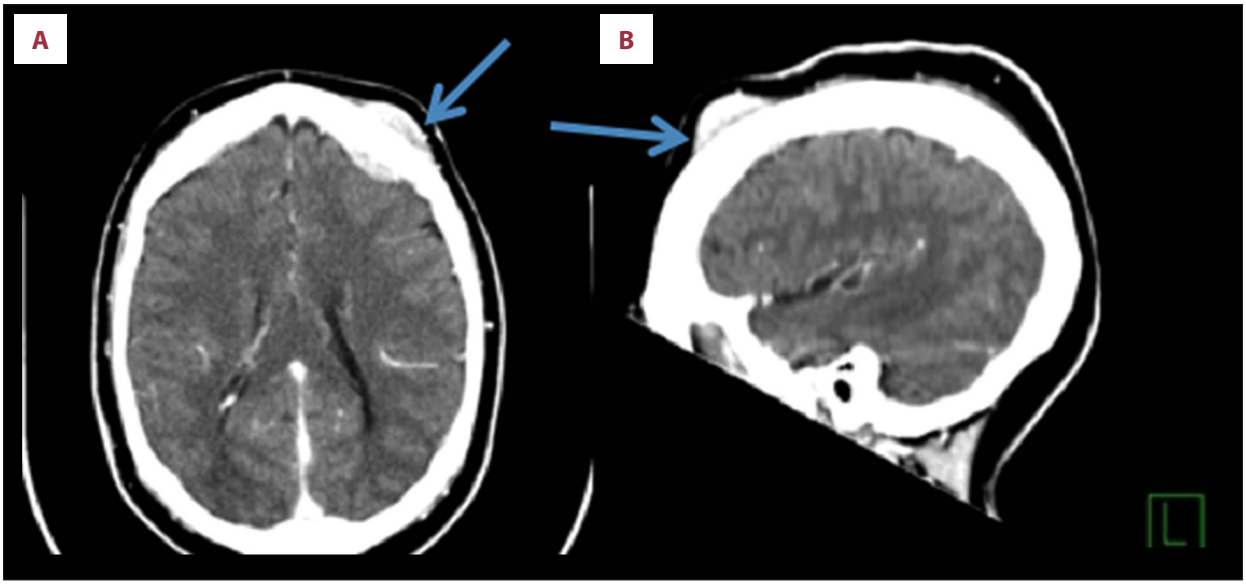

Figure 1. (**A**,**B**) Computed tomography scan of head shows prominent left frontal mass extending through the skull bones. The arrows depict the skull mass.

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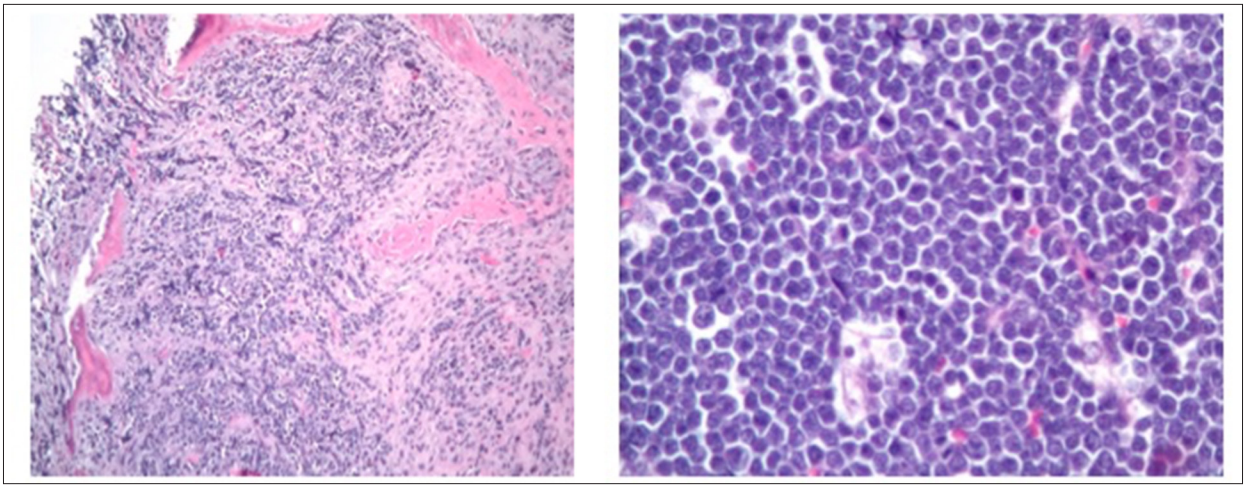

Figure 2. Pathology of skull lesions. Low power shows infiltration of cranium by Burkitt cells with bone destruction and reactive new bone formation. High power image shows numerous apoptotic bodies and distinctive nuclear morphology.

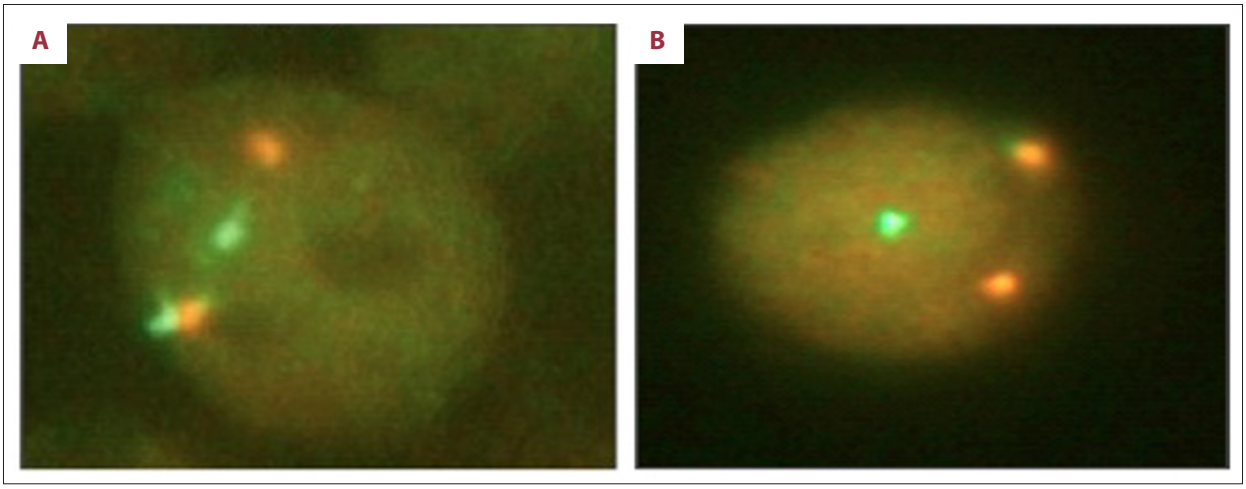

Figure 3. Fluorescent *in-situ* hybridization (FISH) examination of the epidural mass. (**A**) FISH with IGH/MYC t(8;14) shows one orange (MYC), one green (IGH), and one fusion (IGH/MYC) signal (1000×). (**B**) FISH of epidural mass sample shows BCL6 translocation: one orange, one green and one fusion signal.

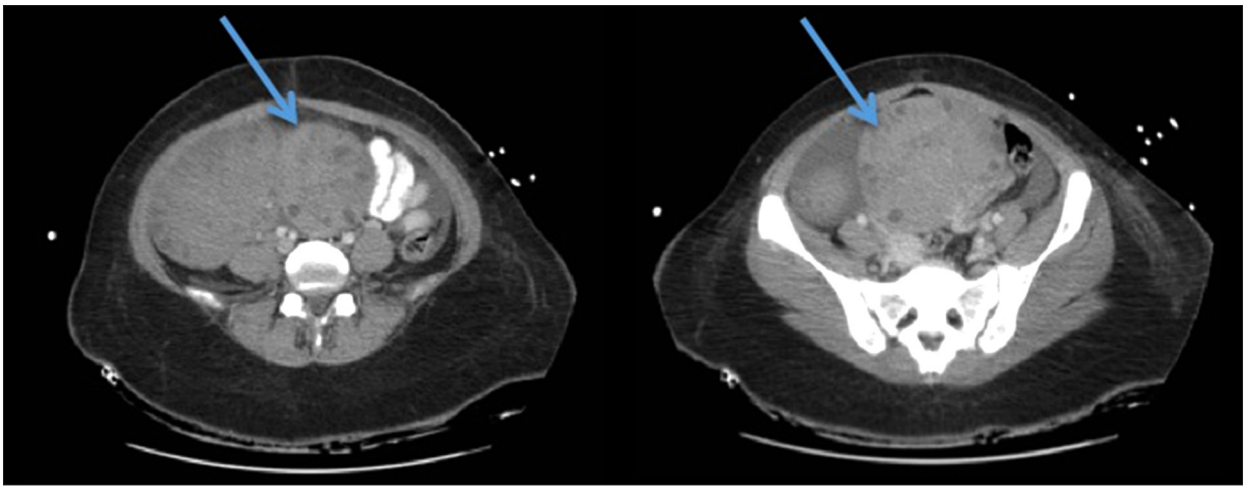

Figure 4. Computed tomography scan of abdomen/pelvis shows the adnexal mass (depicted by the arrows).

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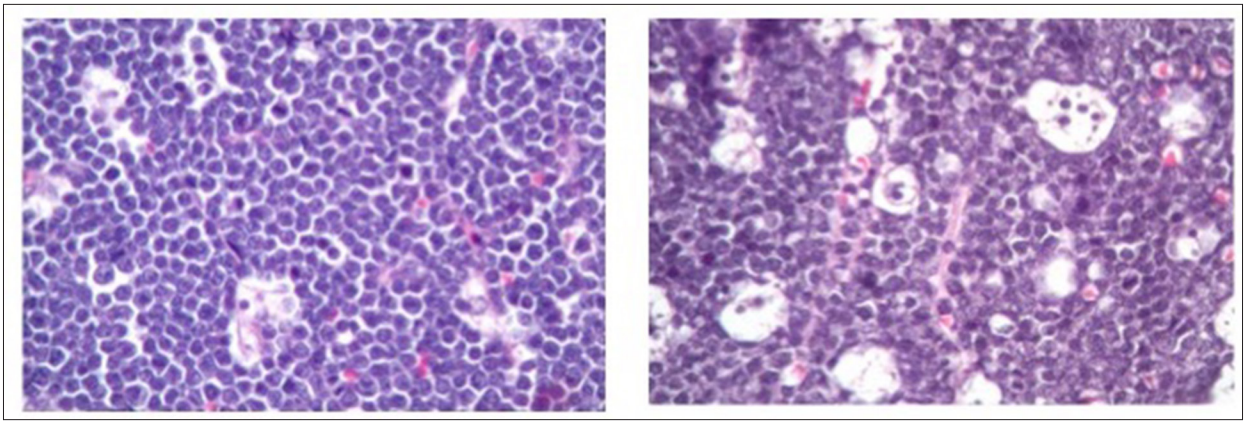

Figure 5. Pathology of bone marrow. Diffuse neoplastic proliferation of atypical lymphoid cells showing a "starry sky" pattern. This characteristic appearance is due to the presence of abundant benign histiocytes engulfing nuclear debris that accumulates from apoptosis of Burkitt cells.

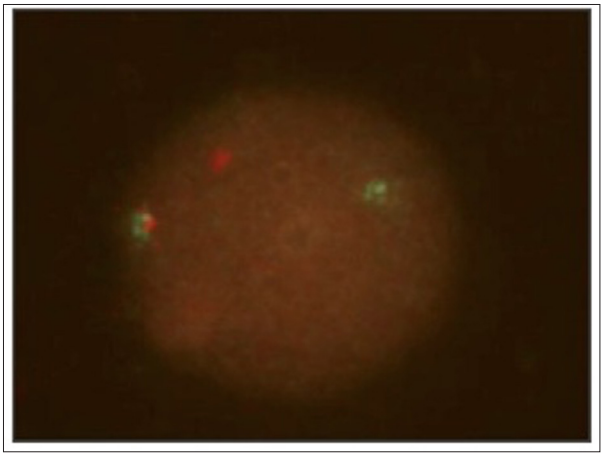

Figure 6. Fluorescent *in-situ* hybridization examination of bone marrow sample. Probe with BCL6 (3q27) breakpoint were used and translocation was found: one orange, one green, and one fusion signal.

posterior nasopharyngeal wall and moderate lymphadenopathy in bilateral anterior triangle of the neck. Hyperuricemia resolved, and the patient clinically improved in a few days.

A bone marrow biopsy was performed. Histology revealed diffuse infiltration by a monotonous and mitotically active population of intermediate-sized lymphoid cells with basophilic cytoplasm and multiple nucleoli. These cytologic details combined with features of a starry sky pattern were reminiscent of a Burkitt lymphoma (Figure 5). Immunohistochemical stains were positive for CD43, CD20, and CD10, and negative for cyclin D1. Additionally, Ki67 showed a proliferative index of >95%. FISH from the bone marrow biopsy was positive for BCL6(3q27) translocation (Figure 6) and cytogenetic studies showed t(3: 14). Cytogenetic analysis of the bone marrow revealed 46,XX,dup(1)(q43q12),t(3;14)(q27;q32) [4]/ 46,idem,del(6)(q15q23) [2]/, 46,XX,dup(1)(q21q41),t(3;14)(q27;q32) [10]/ 46,XX [4]. A diagnosis of stage IV high grade B-cell lymphoma (HGBL) with MYC and BCL6 rearrangements was made. The International Prognostic Index (IPI) score was calculated at 3 (high intermediate).

The patient was then transferred to another institution where she received R-EPOCH (rituximab, etoposide phosphate, prednisone, vincristine, cyclophosphamide, and doxorubicin) [6] and achieved complete remission 9 months after diagnosis.

During the hospital stay, it was discovered that the patient had an admission in a neighboring hospital around 4 weeks prior to the current presentation. Review of medical records revealed that the patient was referred to the hospital after hypercalcemia was found on routine laboratory testing. The patient was asymptomatic at that time. A CT scan performed during that admission revealed a left adnexal mass measuring 5.8×4.2×5.5cm and right adnexal mass measuring 6.1×5.5×7.4 cm. The patient was managed with intravenous fluids with subsequent normalization of the calcium levels and was discharged. The patient was then lost to follow-up until the presentation in our institution.

Discussion

In the 2016 WHO classification, "gray zone lymphomas" have been assigned a new category termed high grade B-cell lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangement. This category includes lymphomas with a gene expression profile (GEP) intermediate between molecular BL and non-molecular BL (most of which are DLBCL) [2].

Double-hit lymphomas (DHL) are characterized by MYC translocation and either a BCL2 or BCL6 translocation. DHL involving MYC and BCL2 translocation occur in around 5% cases

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Table 1. Literature review of the extranodal presentation in double-hit lymphoma.

Diagnosis	Demographics	Cytogenetics (by FISH or otherwise specified)	Location	Treatment and Outcome
DLBCL [11]	1 patient – HIV negative	BCL2 translocation BCL6 translocation	CNS, bone, marrow, peripheral blood	Died in progression
DLBCL [10]	3 patients	MYC (break apart probe) BCL6 rearrangement	Intestine, stomach	CHOP, died of disease
DLBCL [12]	1 patient	MYC translocation BCL6 rearrangement	Sacrum, lymph nodes, stomach	R-CHOP therapy.
DLBCL [9]	3 patients	2 patients – Burkitt lymphoma (MYC positive) 1 patient – DLBCL (MYC/BCL2 positive)	Ovaries	1 patient alive with disease 2 patients died with disease
Burkitt lymphoma [8]	1 patient	C-MYC by southern blot	Ovaries	R-CHOP
DHL [7]	1 patient	MYC translocation BCL2 translocation	Skull, nasopharynx, CNS	Patient died one month after diagnosis
DHL/THL [13]	27 patients	MYC BCL2 BCL6	Ovary (1), bone (2), stomach (3), CNS (2), other extranodal sites.	More extranodal sites for DHL/THL (23/27 Patients)
DHL/THL [14]	5 patients	BCL2/IGH rearrangement MYC rearrangement BCL6 rearrangement	Adrenal mass, supraclavicular LN, subareolar breast mass, bone marrow and peripheral blood, peripancreatic LN and celiac trunk LN	R-EPOCH Hyper-CVAD R-Hyper CVAD DA-EPOCH-R
BCL-U with features intermediate between large B-cell lymphoma and Burkitt Lymphoma [1]	2 patients	MYC/BCL2/BCL6 rearrangement (1 patient) MYC/BCL2 rearrangement (1 patient)	Patient 1 – tonsil mass, frontal bone of skull. Patient 2 – LN, rib lesions	Patient 1 – declined treatment and died Patient 2 – partial response with R-ESHAP
BCLU (intermediate between BL and DLBCL) [4]	1 patient	BCL6/MYC juxtaposition	Bone marrow	Good prognosis – patient did well after receiving RCHOP and then R-CODOXM-IVAC
Large B-cell lymphoma [15]	6 patients	MYC translocation BCL6 (3q27)	Nasopharynx, cervical LN, liver, RPLN	R-CHOP, 3 alive, 1 dead, 2 N/A

CNS – central nervous system; diffuse large B-cell lymphomas, DLBCL – double-hit lymphoma/triple-hit lymphoma, DHL/THL; FISH – fluorescent *in-situ* hybridization; LN – lymph node.

of DLBCL and have a median survival of about 8 months [3]. Most of these cases present with extranodal involvement, including involvement of bone marrow, peripheral blood, pleural effusion, stomach, ascites, and bones [8]. DHL with MYC and BCL6 translocation are also very aggressive tumors and tend to have extranodal involvement, as illustrated in Table 1. Common extranodal sites with MYC/BCL2 or MYC/BCL6 translocations include liver, central nervous system, ribs, breast, intestine, sacrum, and stomach [1,8–13].

Literature search was performed to look into "double-hit/triple-hit" lymphomas with large B-cell morphology/DLBCL/BCL-U/BL morphology (Table 1). Historically, lymphomas harboring BCL6 translocations tend to present more with extranodal sites when compared to BCL2 [14]. But in the case of DHL harboring BCL6 translocation, the correlation is not well defined. For example, in a small series of DHL with MYC/BCL2 translocations, extranodal involvement was reported in 85–95% of cases with bone marrow being the most common site [15–17]. On the

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other hand, Pillai et al. demonstrated extranodal involvement in more than 75% of their small series of MYC/BCL6 DHL [5]. Furthermore, Turakhia et al. reported up to 50% involvement of extranodal sites, mainly soft tissue, in their series [13]. Involvement of extranodal sites carries a worse prognosis across the board.

Our search yielded only 2 cases of "double-hit/triple-hit" lymphomas involving the skull [1,7]. One case was a MYC/BCL2 translocation and involved the skull, nasopharynx and central nervous system, and the patient died 1 month after diagnosis [7]. The other case involved the skull and tonsil and had MYC/BCL2/BCL6 rearrangement and the patient declined treatment and died [1]. Four cases have been reported with involvement of the ovaries [8,18]. Our case had bilateral adnexal lesions but was not biopsied.

MYC has an important role in cell-cycle progression, apoptosis, and cellular transformation via induction of genes involved in cell cycle control (such as cyclin D1) and suppression of growth arresting genes. Translocation to IG *loci* results in the control of its expression (it is dysregulated by NF-κb and BCL6) [19]. BCL2 has potent anti-apoptotic functions that lead to a survival advantage of the involved B cells. The aggressive course and chemotherapy resistance of MYC/BCL2 DHLs are related to a synergism between the 2 mechanisms [20]. BCL6 interacts with p53 tumor suppressor gene in germinal center B cell to prevent their apoptosis [21]. Translocation of BCL6 gene leads to its dysregulation which ultimately leads to repression of cell cycle regulators and hence its role in oncogenesis [22]. This explains double-hit lymphomas (DHL) with MYC and either BCL6 or BCL 2 re-arrangement having a more aggressive course than single-hit lymphomas [1,23]. Their median survival is around 8 months compared to 5-year survival of 33% in high-risk DLBCL patient [3]. Moreover, the response to chemotherapy is transient and relapse rate is high [8].

Standard chemotherapy regimens for non-Hodgkin lymphoma, such as R-CHOP, are not used for HGBL/DHL as patients do poorly and relapse [6]. First-line treatment with R-EPOCH significantly reduces the risk of progression compared to R-CHOP (relative risk reduction of 34%) [6]. Other options include R-CODOX-M/IVAC [6]. Another study has shown that using DA-EPOCH gave a median survival of 34 months (compared to 8 months when using R-CHOP) [24]. The use of intensified backbone (DA-EPOCH, Hyper-CVAD, CODOX-M/IVAC) results in significantly higher rate of complete response compared to CHOP backbone [25]. However, no statistically significant improvement in overall survival was seen with consolidative high-dose chemotherapy followed by autologous stem cell transplant (HDT-ASCT) [25,26].

Conclusions

To our knowledge this rare presentation of HGBL with MYC and BCL6 translocation with unusual extranodal locations has only been reported twice in the skull. Our case had involvement of the skull and the adnexa. Clinicians in the future need to be aware of such aggressive lymphomas that frequently involve extranodal sites so that early diagnosis can be made, and correct multi-agent chemotherapy can be initiated in a timely manner.

Conflict of interests

None.

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