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Letters to the Editor

Double-Hit Lymphoma: A Rare Variant

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TO THE EDITOR

Diffuse large B-cell lymphomas (DLBCL) are a heterogeneous group of aggressive lymphomas. Approximately 40% of all B-cell lymphomas have a recurrent reciprocal chromosomal translocation, commonly involving an oncogene and an immunoglobulin loci enhancer. Lymphomas with recurrent chromosomal breakpoints that activate multiple oncogenes, one of which is MYC, are known as "double hit" lymphomas. These chromosomal breakpoints, when present, portend a worse prognosis. Most common double-hit lymphomas involve *MYC* and *BCL2* gene translocations. We describe a very rare case of a patient with DLBCL involving the gene loci *MYC* and *BCL6*.

A 34-year-old male presents to the emergency department with bilateral lower extremity weakness and shooting pain. He was unable to ambulate without using a walker and had suffered multiple falls. He had no significant past medical or surgical history. Computed tomography scan of lumbar spine was normal so an magnetic resonance imaging (MRI) was performed that showed homogeneous hyperintense lesion extending posteriorly from L3-S1 vertebral bodies with obstruction of spinal canal (Fig. 1). The patient underwent L4-L5 laminectomy with resolution of symptoms. He was discharged subsequently with rest of the work-up and treatment planned on an outpatient basis.

Histopathologic evaluation of the biopsy of the lumbar mass revealed the presence of adipose tissue infiltrated by sheets of predominantly medium-sized to large lymphoid cells with round to ovoid nuclei, one to a few conspicuous nucleoli, and variably clumped to fine chromatin (Fig. 2A & 2B). In addition, frequent mitoses, karyorrhectic debris and apoptotic cells were observed, and these findings raised the possibility of shrinkage artifact on the lymphoma cells. By immunohistochemistry, the cells of the infiltrate were show to be positive for CD20 (Fig. 2C), PAX5 (Fig. 2D), MUM1 (Fig. 2E), FOXP1, and weakly positive for BCL2 (Fig. 2F). An immunostain for Ki-67 showed expression in approximately 95% of the lymphoma cells (Fig. 2G), whereas immunostains for CD3, CD5, CD10, BCL6, GCET1, MYC, CD23, cyclin D1, TdT and CD34 were negative. The immunophenotype was indicative of an activated B-cell (ABC) subtype, according to the Choi algorithm. Limited flow-cytometric evaluation identified a mature B-cell population expressing CD19, CD20 and high-density monotypic κ surface immunoglobulin light chains present at 60% of the lymphocytes (less than 0.1% of all CD45-positive events). Cytogenetic (fluorescence *in situ* hybridization: FISH) testing of the tumor were positive for *IGH/MYC* fusion (93%) and *BCL6/3q27* alternate breakpoint locus rearrangement (93%), without a *BCL2/18q21* rearrange-

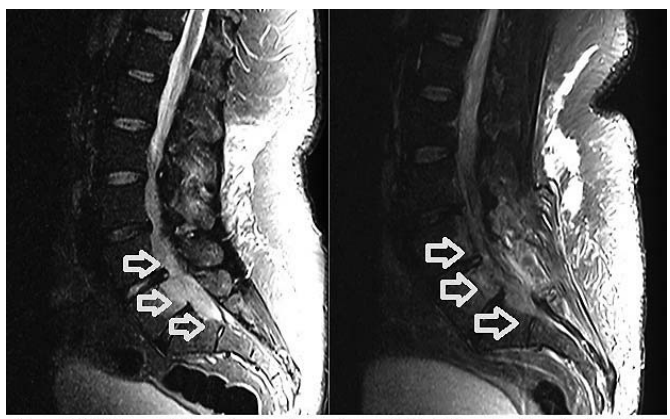

Fig. 1. T2 STIR images of the lumbar spine showing the mass before (*left panel*) and 1 week after (*right panel*) laminectomy. *Arrows* point towards the tumor.

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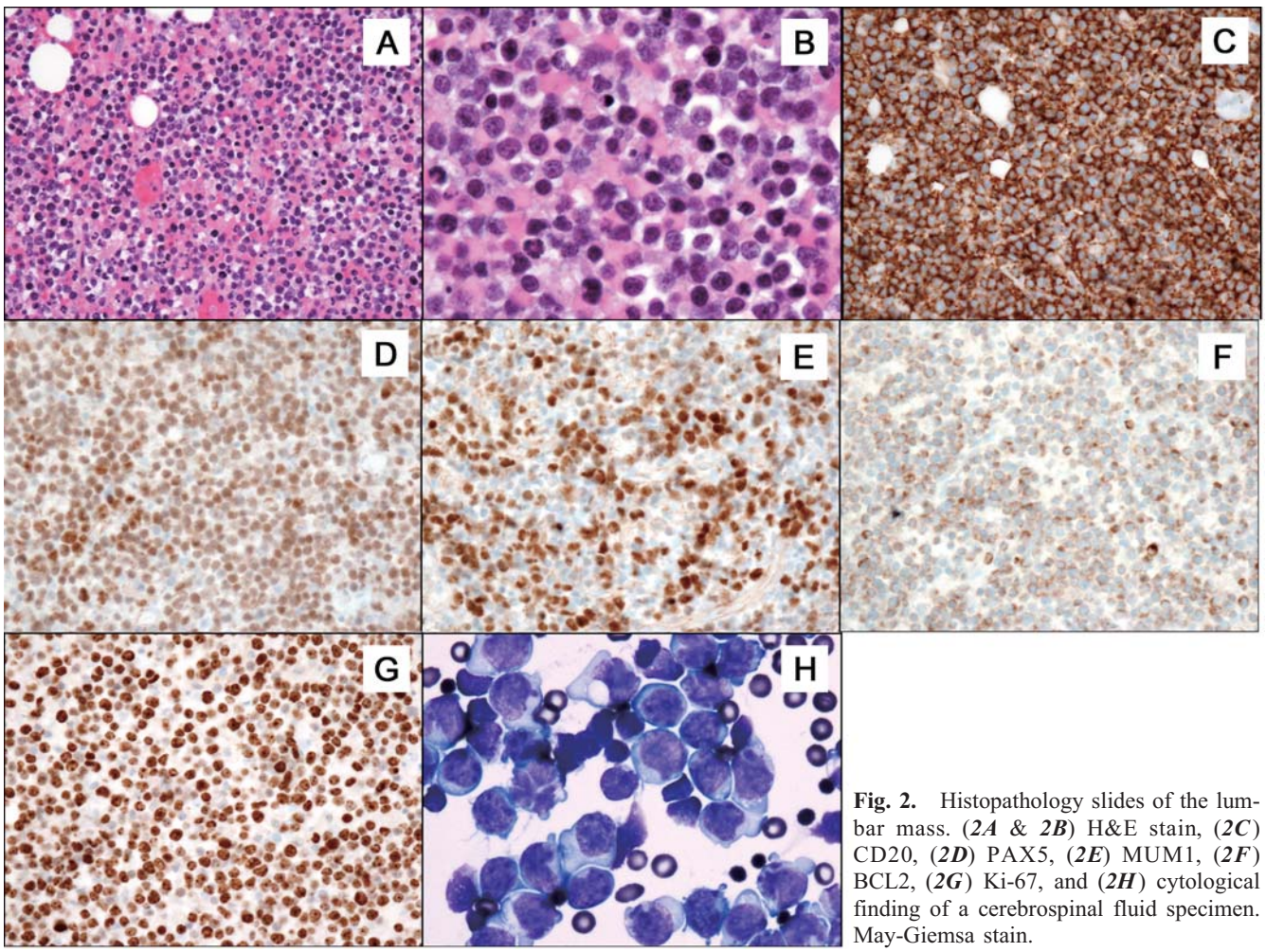

Fig. 2. Histopathology slides of the lumbar mass. (***2A*** & ***2B***) H&E stain, (***2C***) CD20, (***2D***) PAX5, (***2E***) MUM1, (***2F***) BCL2, (***2G***) Ki-67, and (***2H***) cytological finding of a cerebrospinal fluid specimen. May-Giemsa stain.

ment. The overall findings were indicative of a diffuse large B-cell lymphoma with a cytogenetic "double hit". Subsequent evaluation of a cerebrospinal fluid specimen revealed involvement by large lymphoma cells (Fig. 2H).

^{18}Fluorine-labeled fluorodeoxyglucose positron emission tomography scan of the body showed involvement of lymph nodes both above and below the diaphragm, hence conferring the diagnosis of stage IV "double hit" DLBCL. One week later, he presented with return of symptoms and a repeat MRI of spine showed worsening extradural mass. He was treated with dose-adjusted R-EPOCH (rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone). His hospital course was prolonged and fraught with complications like lung and spinal abscess. Currently, the patient is bedridden with a poor prognosis and requires intravenous analgesia with a patient-controlled analgesia device.

New paragraph Double-hit lymphoma refers to a subtype of mature B-cell lymphomas that possess chromosomal translocations involving two oncogene loci, most commonly *MYC/8q24* and *BCL2/18q21*. On rare occasions, it may involve *BCL6/3q27* and *MYC/8q24* gene loci. The Mitelman Database of Chromosome Aberrations in Cancer, a database that contains virtually all published cytogenetic data on various malignancies, mentions about 26 such cases till date (8% of all double-hit lymphomas).[1]

MYC translocation confers a negative prognostic impact on patients treated with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) and CHOP plus rituximab (R-CHOP) regimens.[2] The lymphomas with "double hit" morphology have a more dismal prognosis, even with high-intensity chemotherapy.[3,4] *MYC* gene rearrangement promotes tumor proliferation, and *BCL2/BCL6* protein expression inhibits cell apoptosis, hence producing a lethal combination.

Currently, combination chemotherapy with R-EPOCH is the only treatment regimen that has the potential to induce complete response in a proportion of such patients, although with no overall survival advantage.[5] In a recent multi-center trial involving patients with double-hit lymphomas treated with high-intensity chemotherapy regimens, the progression-free survival and overall survival rates at 2 years were 40% and 49%, respectively.[5] An alternate regimen that has been

recently shown to be effective for penetration into the cerebrospinal fluid consists of rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyperCVAD).[6] This regimen, however, is more cumbersome and has the potential to cause severe toxicity. Recently, Zappasodi *et al*., showed that heat-shock protein 105 (HSP105/HSPH1) is preferentially expressed in high-grade B-cell lymphomas and its inhibition downregulates the expression of *MYC* and *BCL-6*, which inhibits tumor growth *in vivo*.[7] This suggests its potential role as a therapeutic target for treatment of such aggressive B-cell lymphomas.

Additional research to identify diagnostic tests to further characterize the biology of these rare tumors are under way. Until then, it seems imperative to test all aggressive B-cell lymphomas for multiple breakpoint activations by FISH.

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