Case Study

B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and mantle cell lymphoma

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Abstract: The expression of cyclin D1 in diffuse large B-cell lymphomas has been reported in the literature several times. However, cases with the t(11;14)(q13;q32) are very uncommon. Herein, we present two cases of diffuse large B-cell lymphoma with the t(11;14)(q13;q32) and cyclin D1 expression, *BCL6* rearrangement and *BCL2* amplification, but negative for SOX11 expression. Although presence of the t(11;14)(q13;q32) is a hallmark of mantle cell lymphoma, it can also be seen in diffuse large B-cell lymphoma, sometimes as a secondary aberration.

Keywords: Diffuse large B-cell lymphoma, cyclin D1, t(11;14)(q13;q32)

Introduction

The t(11;14)(q13;q32) results in deregulated expression of cyclin D1 protein and is present in over 95% of mantle cell lymphomas, as well as being the most common translocation in plasma cell myeloma [1, 2]. Cyclin D1 is a nuclear protein encoded by the *CCND1* gene located on chromosome 11q13, and it plays a key role in promoting the transition from G1 to S phase in cell division. This transition is achieved by the binding of cyclin D1 to cyclin-dependent kinases CDK4 and 6, which activate the transcription factor E2F by phosphorylating the retinoblastoma protein, and promote the entry into S phase [3–5]. Therefore, overexpression of cyclin D1 is implicated in the development of various carcinomas and lymphoid malignancies including mantle cell lymphoma, plasma cell myeloma, hairy cell leukemia and, rarely, diffuse large B-cell lymphoma [6, 7]. Interestingly, the t(11;14)(q13;q32) is not seen in hairy cell leukemia, which points toward the presence of alternative mechanisms for the overexpression of cyclin D1 [8].

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, accounting for 25-35% of adult non-Hodgkin lymphomas in developed countries, and even higher in developing countries. Rearrangement of the 3q37 chromosomal region involving the *BCL6* gene is the most common translocation in DLBCL, present in about 30% of cases [1]. The presence of cyclin D1 expression in DLBCL ranges from 0-15% in various studies [7, 9–11]. However, the t(11;14)(q13;q32) is rare in DLBCL [9, 12, 13]. Herein, we describe two

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cases with typical DLBCL morphology, cyclin D1 expression due to the t(11;14)(q13;q32), *BCL6* rearrangement and *BCL2* amplification.

Methods

We used a Leica BOND III autostainer (Leica, Buffalo Grove, IL) and followed the protocols recommended by the company to stain paraffin-embedded tissue sections. Fluorescence *in situ* hybridization (FISH) cytogenetics was also performed on paraffin-embedded tissue sections. We examined interphase nuclei using the following probes (Abbott Molecular, Abbott Park, IL): Vysis LSI *IGH/CCND1* dual color, dual fusion translocation probe; Vysis LSI *BCL6* (ABR) dual color break-apart rearrangement probe, Vysis LSI *IGH/BCL2* dual color, dual fusion translocation probe; Vysis LSI *IGH/MYC/CEP8* tri color dual fusion probe; and the Vysis LSI *MYC* dual color break-apart rearrangement probe.

Case Report

CASE 1

A 56-year-old female presented with fever, sweats, and weakness in August of 2015. A workup revealed elevated liver function tests. A PET/CT scan showed multiple enlarged and metabolically-active lymph nodes in the right supraclavicular region and mediastinum, as well as foci in the right lobe of the liver and the right ilium. Flow cytometric studies performed on peripheral blood and pleural fluid showed a clonal B-cell population. A bone marrow biopsy showed extensive involvement by DLBCL. One week later, a liver biopsy also showed involvement by DLBCL. The patient was started on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), and achieved a complete remission. In March of 2016, she developed back pain and a PET/CT scan demonstrated multiple hypermetabolic areas in the liver and left inguinal lymph nodes consistent with recurrent disease. In June of 2016, a bone marrow biopsy showed minimal residual B-cell lymphoma. She subsequently received aggressive chemotherapy without benefit. In October of 2016 and January of 2017, bone marrow biopsies showed no evidence of lymphoma by morphology, flow cytometry or cytogenetic studies. However, a lymph node biopsy performed in March of 2017 showed DLBCL with a non-germinal center cell phenotype. The patient died of progressive disease a few weeks later.

Flow cytometric studies performed on peripheral blood and pleural fluid showed a clonal B-cell population expressing CD5, CD19, CD20, CD22, and kappa light chains. A bone marrow biopsy showed extensive involvement by DLBCL and immunostains demonstrated the cells to be positive for CD20 with a subset positive for cyclin D1, but negative for SOX11 (Fig. 1). Flow cytometry of the bone marrow showed a kappa-restricted B-cell population expressing CD5 (dim), CD19, CD20 and CD22. FISH cytogenetic analysis revealed one cell with a *CCND1/IGH* fusion signal. One week later, a liver biopsy showed involvement by DLBCL expressing CD20, PAX5, cyclin D1 (subset) and CD5 (subset), whereas CD3 and SOX11 were negative (Fig. 2). FISH analysis was negative for *IGH/BCL2* fusion, *CCND1/IGH* fusion and *MYC* rearrangement, but an atypical *BCL6* gene rearrangement was detected. In June of 2016, a bone marrow biopsy showed minimal residual B-cell lymphoma and cytogenetic studies showed: 47,XX t(1;7)(p13;q32),del(3)(?q12q21),del(6)(q21q25), t(11;14)(q13;q32), add(13)(p11.1), +18[2]/46XX[18]. A lymph node biopsy performed in March of 2017 showed DLBCL with a non-germinal center phenotype. The cells were positive for CD20, PAX-5, CD5 (subset), MUM1, BCL6, BCL2, cyclin D1, MYC (30%) and Ki-67 (>95%), and were negative for CD3, CD10, CD43, CD21, CD30 and SOX11 (Fig. 3). FISH studies were positive for a variant *CCND1/IGH* fusion gene rearrangement in 68% of cells, 5' *BCL6* loss, and gains of *IGH* and *BCL2*. Flow cytometry studies of the peripheral blood showed 27% abnormal large B-cells expressing CD19, CD20, CD22, CD24, CD38

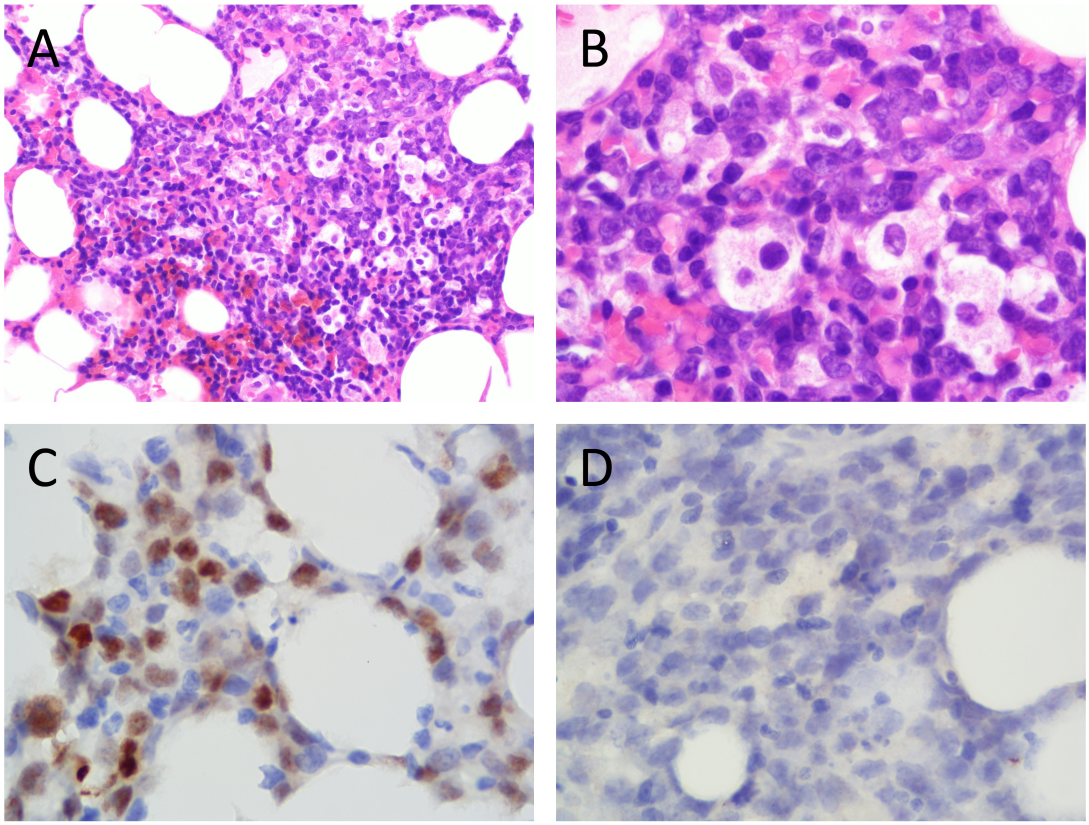

Figure 1: Bone marrow with a large cluster of large lymphoma cells with tingible-body macrophages admixed. H&E, 400x (A), H&E, 1000x (B), cyclin D1, 1000x (C), and SOX11, 1000x (D).

and CD5, with kappa light chain restriction, whereas CD10, CD11c, CD23, CD34 and lambda light chain were negative.

CASE 2

A 75-year-old male presented with a rapidly-enlarging left neck mass in July of 2017. A biopsy of the mass showed involvement by DLBCL with a germinal center cell phenotype. A subsequent bone marrow biopsy did not show evidence of involvement by lymphoma. He was treated with R-CHOP, but was lost to follow-up.

A biopsy of the left neck mass showed DLBCL. The lymphoma cells were positive for CD20, cyclin D1, BCL2, BCL6 and Ki-67 (65%), and negative for CD3, CD5, CD10, MUM1, C-MYC, SOX11, EBER and CD30 (Fig. 4). FISH analysis showed a *BCL6* rearrangement in 88% of cells, and a *CCND1/IGH* rearrangement was seen in 78% of cells. Amplification of *BCL2* was observed in 100% of cells, but *BCL2* and *MYC* rearrangements were not present. Flow cytometry showed a clonal B-cell population positive for CD22, HLA-DR (bright), CD38, CD45 (moderate-bright), with partial expression of CD19 (dim), CD20 (dim), FMC7 and CD23 (dim), and weak expression of CD5. The kappa to lambda ratio was 91:<1, and the cells were negative for CD10.

Discussion

We present two cases of DLBCL with the t(11;14)(q13;q32), *BCL6* rearrangement and *BCL2* amplification. The main differential diagnosis in these

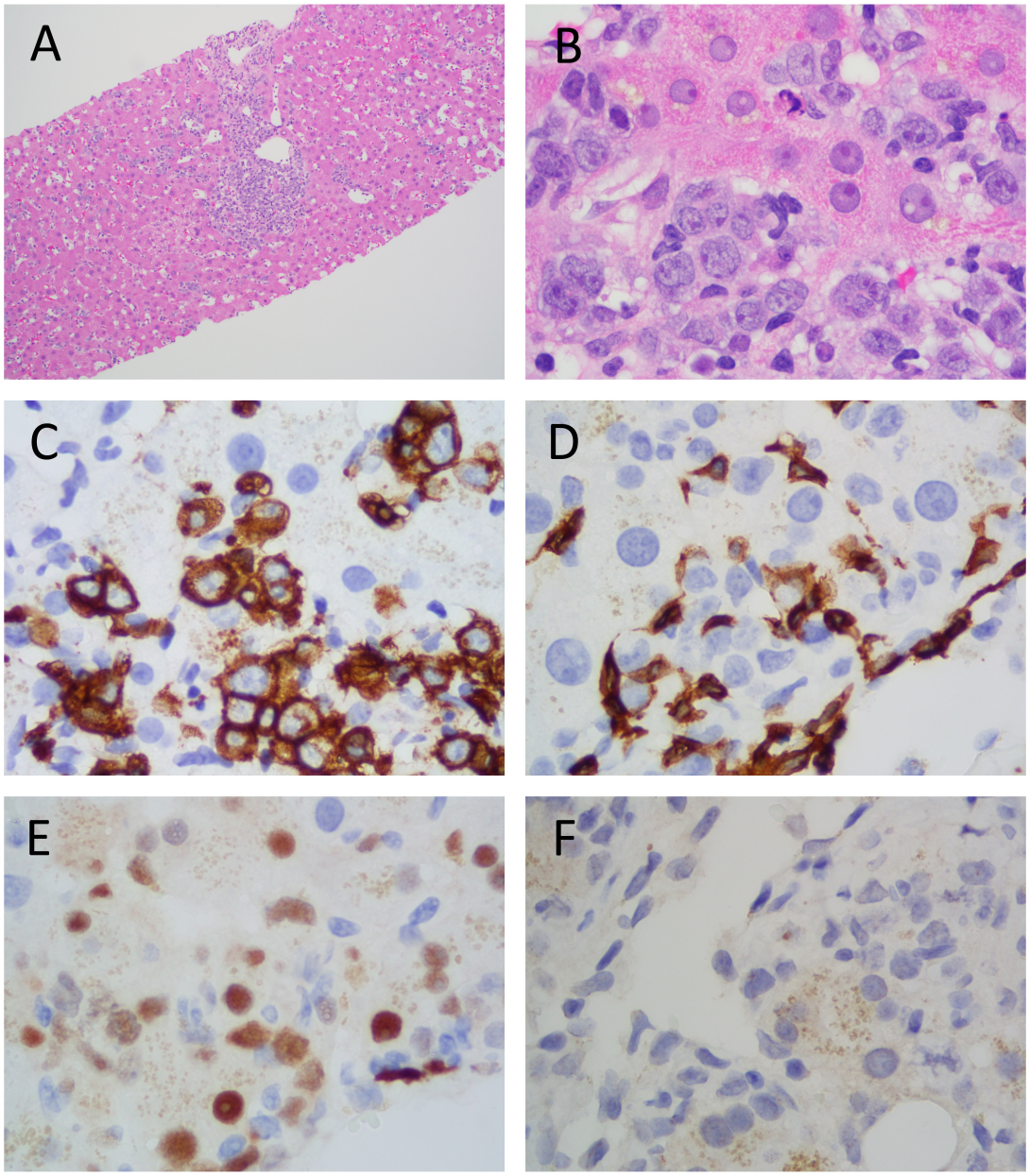

Figure 2: Liver with focal lymphoid infiltrates. H&E 100x (A), pleomorphic large cells with irregular nuclear contours and multiple nucleoli, H&E, 1000x (B), CD20, 1000x (C), CD3, 1000x (D), cyclin D1, 1000x (E), and SOX11, 1000x (F).

cases is a pleomorphic or blastic mantle cell lymphoma [1]. Although more than 95% of mantle cell lymphomas are positive for cyclin D1, the presence of cyclin D1 is not specific for mantle cell lymphoma and can be found in other entities. About 12% of mantle cell lymphomas express BCL6, which is a transcription factor that plays a crucial role in germinal center formation [14–16]. However, *BCL6* re-

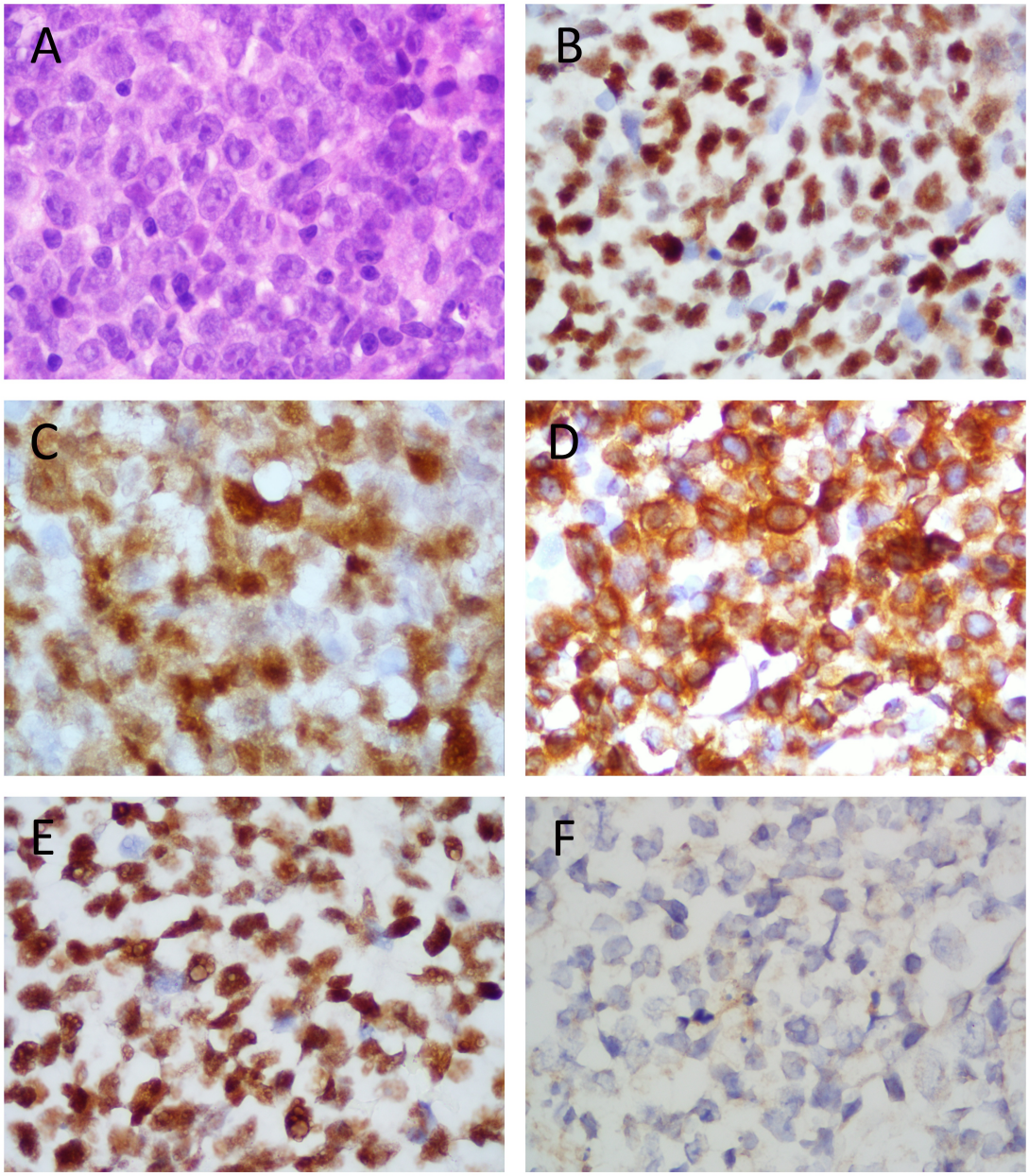

Figure 3: Lymph node with large pleomorphic cells with irregular nuclear contours and multiple nucleoli. H&E 1000x (A), PAX-5, 1000x (B), cyclin D1, 1000x (C), BCL2, 1000x (D), BCL6, 1000x (E), and SOX11, 1000x (F).

arrangements in mantle cell lymphoma, as opposed to DLBCL, are extremely uncommon and have only been reported in a few cases [17].

The presence of cyclin D1 expression in diffuse large B-cell lymphoma has been reported several times [18, 19]. However, the presence of t(11;14)(q13;q32) has been reported in only a few cases [9, 12, 13], including a case that acquired the translocation later, which is a phenomenon also described in other lymphomas [12, 20].

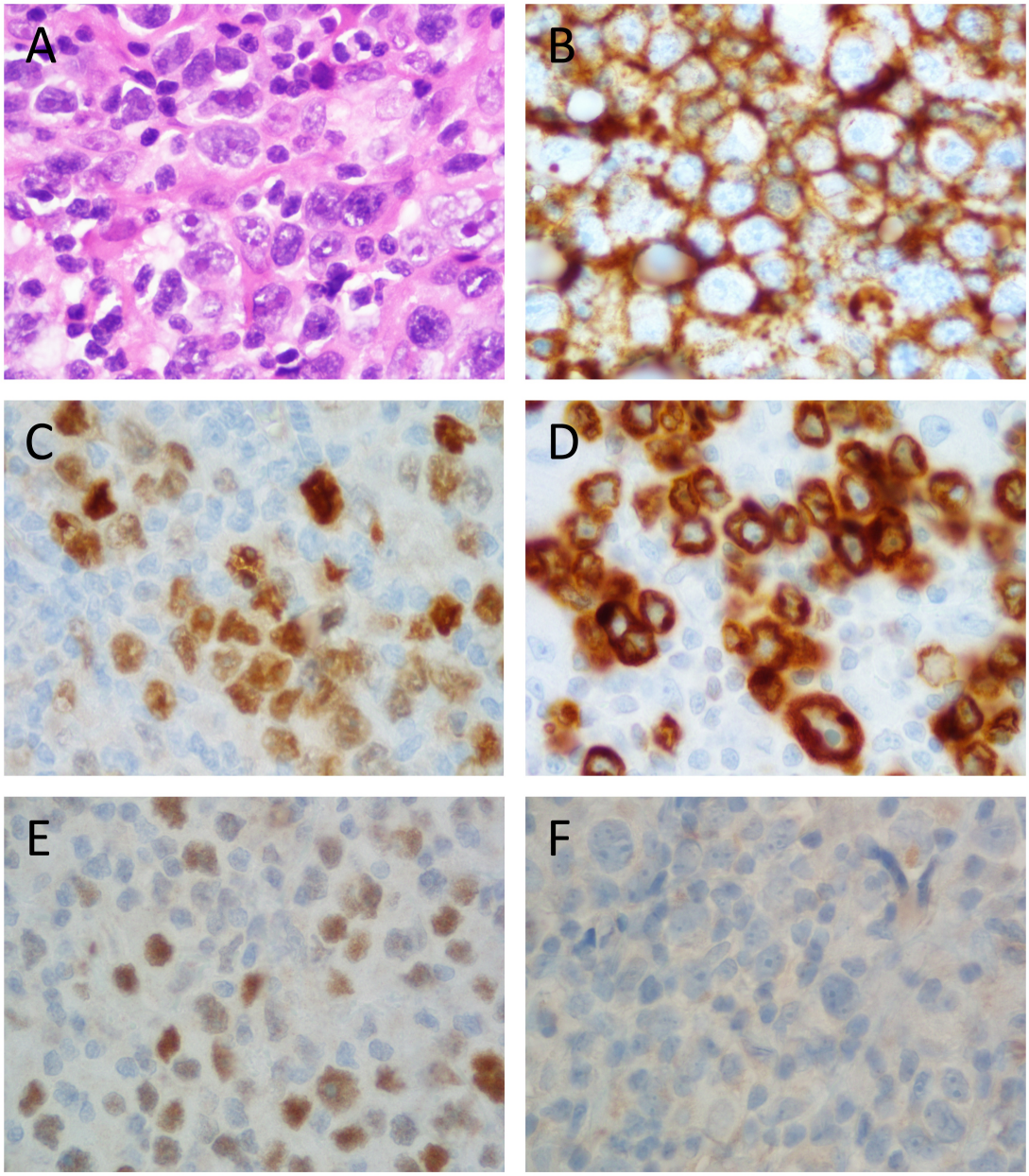

Figure 4: Left neck mass with pleomorphic large cells and admixed small lymphocytes. H&E, 1000x (A), CD20, 1000x (B), cyclin D1, 1000x (C), BCL2, 1000x (D), BCL6, 1000x (E), and SOX11, 1000x (F).

In a study by Ehinger *et al* [9], 4.3% of DLBCL were positive for cyclin D1, and the presence of t(11;14)(q13;q32) was demonstrated in one of the ten cases positive for cyclin D1. In another study by Juskevicius *et al* [13], cyclin D1 was present in 5% of DLBCL and one case showed a t(11;14)(q13;q32), whereas another case had a complex t(4;11;14). The former case was positive for BCL6 but not the latter. MUM1 was positive in both, and CD5 and SOX11 were negative. Array comparative genomic

hybridization (aCGH) found an overlap between the case with t(11;14)(q13;q32) and other cases of DLBCL. However, the profile of the case with the complex translocation was more ambiguous. Al-Kawaaz *et al* [12] also reported 2 cases of DLBCL with *CCND1* and *BCL6* rearrangements. In addition to cyclin D1, both cases were positive for BCL6 and MUM1, but negative for SOX11. Furthermore, one case showed EBER positivity, which strongly favors DLBCL over mantle cell lymphoma.

Our first case showed a t(11;14)(q13;q32) in the bone marrow and lymph node but not in the liver. Even though this case showed CD5 positivity, the presence of a *BCL6* rearrangement and lack of SOX11 expression favor the diagnosis of DLBCL. Cyclin D1 was present in only a subset of cells in the bone marrow and liver, whereas in the lymph node it was present in most cells. This discrepancy in cyclin D1 expression suggests that the t(11;14)(q13;q32) was a secondary abnormality rather than a primary event. Although there are no findings that are specific for diffuse large B-cell lymphoma or mantle cell lymphoma, the centroblastic morphology coupled with the immunohistochemical and cytogenetic findings are very useful tools to differentiate between DLBCL and mantle cell lymphoma.

It should never be assumed that a lymphoma with t(11;14)(q13;q32) is a mantle cell lymphoma, especially when the morphology and immunohistochemistry are not typical. Cases with large pleomorphic cells pose a diagnostic challenge and it is important to keep in mind that DLBCL can have a t(11;14)(q13;q32) as primary or secondary aberration.

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References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (Eds): WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues (Revised 4th Edition). IARC: Lyon 2017.
2. Specht, K. Different Mechanisms of Cyclin D1 Overexpression in Multiple Myeloma Revealed by Fluorescence in Situ Hybridization and Quantitative Analysis of mRNA Levels. Blood. 2004;104(4): 1120-1126.
3. Baldin, V, Lukas J, Marcote MJ, Pagano M, Draetta G. Cyclin D1 Is a Nuclear Protein Required for Cell Cycle Progression in G1. Genes Dev. 1993;7(5): 812-821.
4. Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell lymphoma. J Clin Invest. 2012;122(10): 3416-3423.
5. Quintanilla-Martinez L, Davies-Hill T, Fend F, et al. Sequestration of p27Kip1 protein by cyclin D1 in typical and blastic variants of mantle cell lymphoma (MCL): implications for pathogenesis. Blood. 2003;101(8): 3181-3187.
6. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG.. Minireview: Cyclin D1: Normal and Abnormal Functions. Endocrinology. 2004;145(12): 5439-5447.
7. Zukerberg LR, Yang WI, Arnold A, Harris NL. Cyclin D1 Expression in Non-Hodgkin's Lymphomas: Detection by Immunohistochemistry. Am J Clin Pathol. 1995;103(6): 756-760.
8. de Boer CJ, Kluin-Nelemans JC, Dreef E, et al. Involvement of the CCND1 Gene in Hairy Cell Leukemia. Ann Oncol. 1996;7(3): 251-256.
9. Ehinger M, Linderoth J, Christensson B, Sander B, Cavallin-Ståhl E. A Subset of CD5- Diffuse Large B-Cell Lymphomas Expresses Nuclear Cyclin D1 With Aberrations a the CCND1 Locus. Am J Clin Pathol. 2008;129(4): 630-638.
10. Rodriguez-Justo M, Huang Y, Ye H, et al. Cyclin D1-Positive Diffuse Large B-Cell Lymphoma. Histopathology. 2008;52(7): 900-903.
11. Vela-Chávez T, Adam P, Kremer M, et al. Cyclin D1 Positive Diffuse Large B-Cell Lymphoma Is a Post-Germinal Center-Type Lymphoma without Alterations in the CCND1 gene Locus. Leuk Lymphoma. 2011;52(3): 458-466.
12. Al-Kawaaz M, Mathew S, Liu Y, et al. Cyclin D1-Positive Diffuse Large B-Cell Lymphoma With IGH-CCND1 Translocation and BCL6 Rearrangement: A Report of Two Cases. Am J Clin Pathol. 2015;143(2): 288-299.

13. Juskevicius D, Ruiz C, Dirnhofer S, Tzankov A. Clinical, Morphologic, Phenotypic, and Genetic Evidence of Cyclin D1-Positive Diffuse Large B-Cell Lymphomas with CYCLIN D1 Gene Rearrangements. Am J Surg Pathol. 2014;38(5): 719-727.
14. Camacho F, García JF, Cigudosa JC, et al. Aberrant Bcl6 Protein Expression in Mantle Cell Lymphoma. Am J Surg Pathol. 2004;28(8): 1051-1056.
15. Gualco G, Weiss LM, Harrington WJ Jr, Bacchi CE. BCL6, MUM1, and CD10 Expression in Mantle Cell Lymphoma. Appl Immunohistochem Mol Morphol. 2010;18(2): 103-108.
16. Palomero J, Vegliante MC, Eguileor A, et al. SOX11 defines two different subtypes of mantle cell lymphoma through transcriptional regulation of BCL6. Leukemia. 2015;30(7): 1596-1599.
17. Miura I, Ohshima A, Chubachi A, et al. BCL6 Rearrangement in a Patient with Mantle Cell Lymphoma. Ann Hematol. 1997;74(5): 247-250.
18. Ok CY, Xu-Monette ZY, Tzankov A, et al. Prevalence and Clinical Implications of Cyclin D1 Expression in Diffuse Large B-Cell Lymphoma (DLBCL) Treated with Immunochemotherapy: A Report from the International DLBCL Rituximab-CHOP Consortium Program. Cancer. 2014;120(12): 1818-1829.
19. Schneider A, Meyer P, DiMaio D, Fu K. Diffuse Large B-Cell Lymphoma with Both CD5 and Cyclin D1 Expression a Case Report and Review of the Literature. J Hematop. 2010;3(4): 145-148.
20. Brito-Babapulle V, Ellis J, Matutes E, et al. Translocation t(11;14)(q13;q32) in Chronic Lymphoid Disorders. Genes Chromosomes Cancer. 1992;5(2): 158-165.