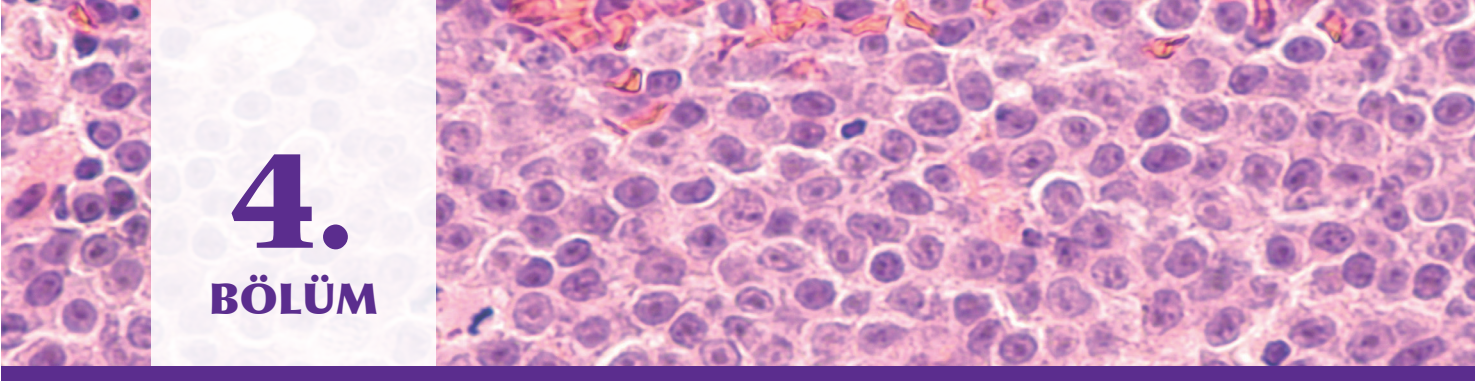

4.
BÖLÜM

DİFFÜZ BÜYÜK B HÜCRELİ LENFOMA, NOS

Saime RAMADAN [1]

GİRİŞ

Diffüz büyük B hücreli lenfoma (DBBHL) tüm dünyada en sık görülen agresif bir non-Hodgkin lenfoma tipidir. Morfolojik, moleküler ve klinik çalışmalar ile DBBHL spesifik alt gruplara ayrılmıştır. Dünya Sağlık Örgütü (DSÖ)'nün 2017 revize hematopoetik ve lenfoid doku tümörlerinin klasifikasyonuna göre spesifik bir grupta yer almayan heterojen olgular, DBBHL- başka şekilde sınıflandırılmamış (NOS) olarak kategorize edilmiştir (1), (Tablo 1).

DBBHL'da izlenen heterojen morfoloji, farklı hücresel orijini, farklı patogenezi veya düşük dereceli bir lenfomadan transformasyonu yansıtmaktadır. Hastalığın agresif seyrine karşın hastaların başlangıç tedavisine yanıtı genellikle iyidir ve 5 yıllık ortalama sağ kalım %60-70 olarak bildirilmiştir (2).

DBBHL orta büyüklükte veya iri neoplastik B hücrelerinin diffüz proliferasyonu olarak tanımlanır. Neoplastik B hücre çekirdekleri normal makrofaj çekirdekleri ile eşit veya büyük, normal lenfosit çekirdeklerinin ise en az iki katı büyüklüğündedir (1).

2017 DSÖ sınıflamasında bir önceki 2008 DSÖ sınıflamasından farklı olarak DBBHL hücre orijinine göre germinal merkez B hücre (GMB) veya postgerminal merkez B hücre (post GMB) veya aktive B hücreli (ABC) olarak kategorize edilmiş ve patoloji raporlarında belirtilmesi gerektiği vurgulanmıştır. Germinal merkez (GM) kaynaklı DBBHL, post germinal merkez kaynaklı DBBHL'lara göre daha iyi surviye sahiptir (3,4).

Epidemiyoloji

DBBHL, NOS gelişmiş ülkelerde erişkin non-Hodgkin lenfomaların (NHL) %25-35'ini oluştururken, bu oran gelişmekte olan ülkelerde daha yüksektir. DBBHL, NOS erişkin hastalarda median 70'li yaşlarda görülmektedir. Ancak yaş aralığı geniştir ve çocuklarda, gençlerde de görülebilmektedir. Çoğu gibi erkek predominansı vardır ve hastaların %55'i erkektir (5,6).

Etiyoloji

DBBHL, NOS hastalarının büyük çoğunluğu bilinen bir risk faktörü taşımamakta ve de novo (primer) gelişmektedir . Bir kısmı ise düşük dereceli bir lenfomadan (folliküler lenfoma, marjinal zon lenfoma, kronik lenfositik lösemi/ küçük lenfositik lenfoma, lenfoplazmositer lenfoma, nodüler lenfosit baskın Hodgkin lenfoma gibi) transforme olmaktadır (sekonder DBBHL).

[1] Uzm. Dr., Başkent Üniversitesi İstanbul Hastanesi, Patoloji AD, drsaimeramadan@yahoo.com

KAYNAKLAR

1. Swerdlow SH., Campo E., Lee Harris N., Jaffe ES., Pileri SA., Stein H.,Thiele J. (Eds) (2017) - WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (Revised 4th edit). Lyon: International Agency for Research on Cancer (IARC).
2. Li S, Young KH, Medeiros J. Diffuse large B-cell lymphoma. Pathology. 2018, 50(1):74-87.
3. Shipp MA, Ross KN, Tamayo P , et al. Diffuse large cell lymphoma outcome prediction by gene expression profiling and supervised machine learning. Nat Med. 2002; 8(1):68-74.
4. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large B-cell lymphoma. N Engl Med. 2002; 346(25):1937-47.
5. Sant M, Allemani C, Tereanu C, et al. Incidince of hematologic malignancies in Europe by morphologic subtype:results of the HAEMACARE Project. Blood.2010; 116(19):3724-34.
6. Shenoy PJ, Malik N, Nooka A, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Cancer. 2010; 117(11):2530-40.
7. Jaffe ES, Arber DA, Campo E, et al. Hematopathology. St. Louis :Elsevier Saunders; 2017.
8. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin 's lymphomas:distributions of the major subtypes differ by geographic locations . Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 1998; 9:717-20.
9. Yao Z, Deng L, Xu-Monette ZY, et al. Concordant bone marrow involvement of diffuse large B cell lymphoma represents a distinct clinical and biological entity in the era of immunotherapy. Leukemia.2018; 32(2):353-63.
10. Brudno J, Tadmor T, Pittaluga S, et al. Discordant bone marrow involvement in non-Hodgkin lymphoma. Blood. 2016; 127:965-70.
11. Horn H, Staiger AM, Vohringer M, et al. Diffuse large B cell lymphomas of immunoblastic type are a major reservoir for MYC-IGH translocations. Am J Surg Pathol. 2015; 39:61-6.
12. Haralambieva E, Pulford KA, Lamant L, et al. Anaplastic large cell lymphomas of B-cell phenotype are anaplastic lymphoma kinase (ALK) negative and belong to the spectrum of diffuse large B-cell lymphomas. Br J Haematol . 2000;109: 584-91.
13. Korkolopoulou P, Vassilakopoulos T, Millionis V, et al. Recent advances in aggressive large B-cell lymphomas:a comprehensive review. Adv Anat Pathol 2016; 23:202-43.
14. Loddenkemper C, Anagnostopoulos I, Hummel M, et al. Differential Emu enhancer activity and expression of BOB.1/OBF.1, Oct2, PU.1. and immunoglobulin in reactive B-cell populations, B-cell non-Hodgkin lymphomas, and Hodgkin lymphomas. J Pathol 2004; 202:60-9.
15. Slack GW, Steidl C, Sehn LH, et al. CD30 expression in de novo diffuse large B cell lymphoma:a population-based study from British Columbia. Br J Haematol. 2014;167:608-17.
16. Hans CP, Weisenburger DD, Greine TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004; 103:275-82.
17. Barrans SL, Fenton JA, Banham a, et al. Strong expression of FOXP-1 identifies a distinct subset of diffuse large B-cell lymphoma (DLBCL) patients with poor outcome. Blood. 2004; 104:2933-5.
18. Natkunam Y, Zhao S, Mason DY, et al. The oncoprotein LMO2 is expressed in normal germinal –center B cells and in human B-cell lymphomas. Blood. 2007; 109:1636-42.
19. Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed parafin – embedded tissue biopsies. J Clin Oncol. 2015; 33:2848-56.
20. 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 Concortium Program. Cancer. 2014; 120:1818-29.
21. Vela-Chavez 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: 458-66.
22. Hassellblom S, Ridell B, Sigurdardottir M, et al. Low rather than high Ki-67 protein expression is an adverse prognostic factor in diffuse large B-cell lymphoma. Leuk Lymphoma. 2008; 49:1501-9.
23. Yoon DH, Choi DR, Ahn HJ, et al. Ki-67 expression as a prognostic factor in diffuse large B-cell lymphoma patients treated with rituximab plus CHOP. Eur J Haematol. 2010; 85:149-57.
24. Georgiou K, Chen L, Berglund M, et al. Genetic basis of PD-L1 overexpression in diffuse large B-cell lymphomas. Blood. 2016; 127: 3026-34.
25. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403:501-11.
26. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficay of bortezomib plus chemotherapy within molecular sub-types of diffuse large B-cell lymphoma. Blood. 2009; 113: 6069-76.
27. Mathews Griner LA, Guha RA, Shinn P, et al. High-throughput combinatorial screeening identifies drugs that cooperate with ibrutinib to kill activated B-cell –like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci USA. 2014; 111: 2349-54.
28. Nowakowski GS, LaPlant B, Habermann TM, et al. Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas:phase I study.Leukemia. 2011; 25:1877-81.
29. Choi WW, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009; 15:5494-502.

30. Visco C, Li Y, XU-Monette , et al. Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorith for molecular subtype classification in diffuse large B-cell lymphoma: a report from the International DLBCL Rituximab-CHOP Concortium Program Study. Leukemia.2012; 26:2103-13.
31. Karube K, Enjuanes A, Dlouhy I, et al. Integrating genomic alterations in diffuse large B-cell lymphoma identifies new relevant pathways and potential therapeutic targets. Leukemia. 2018;32(3):675-684.
32. Iqbal J, Meyer PN, Smith LM, et al. Distinctive patterns of BCL6 molecular alterations and their functional consequences in different subgroups of diffuse large B-cell lymphoma. Leukemia. 2007; 21:2332-43.
33. Visco C, Tzankov A, Xu-Monette ZY, et al. Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC-status:a report from an International DLBCL rituximab-CHOP Concortium Program Study. Haematologica. 2013; 98:255-63.
34. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol. 2010; 28:3360-5.
35. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood. 2011; 117:2319-31.
36. Xu-Monette ZY, Dabaja BS, Wang X, et al. Clinical features, tumor biology, and prognosis asscociated with MYC rearrangement and Myc overexpression in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Mod Pathol. 2015; 28:1355- 73.
37. Morin RD, Mungall K, Pleasance E, et al. Mutational and structural analysis of diffuse large B-cell lymphoma using whole genome sequencing. Blood. 2013; 122:1256-65.
38. Zhang J, Grubor V, Love CL, et al. Genetic heterogeneity of diffuse large B-cell lymphoma. Proc Natl Acad Sci USA. 2013; 110:1398-403.
39. Young KH, Weisenburger DD, Dave BJ, et al. Mutations in the DNA-binding codons of TP53, which are associated with decreased expression of TRAILreceptor -2, predict for poor survival in diffuse large B-cell lymphoma. Blood. 2007; 110:4396-405.
40. Tan DE, Foo JN, Bei JX, et al. Genome-wide association study of B-cell non-Hodgkin lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. Nat Genet. 2013; 45:804-807.
41. Adams H, Schmid P, Dirnhofer S, et al. Cytokeratin expression in hematological neoplasms:A tissue microarray studyon 866 lymphoma and leukemia cases. Pathol Res Pract. 2008; 204(8):569-73.
42. Yang LH, Ingersoll K, Zhao Y, et al. CD-3 positive diffuse large B-cell lymphoma relapses as CD3-negative large B-cell lymphoma:Loss of aberrant antigen expression in B-cell lymphoma after chemotherapy. Pathol Res Pract. 2018; 214(10):1738-44.
43. King JF, Lam JT. A practical approach to diagnosis of B-cell Lymphomas with diffuse large cell morphology. Arcl Pathol Lab Med.2020; 144(2):160-167.
44. Hsiao SC, Cortada IR, Colomo L, et al. SOX 11 is useful in differentiating cyclin-D1 positive diffuse large B cell lymphoma from mantle cell lymphoma. Histopathology. 2012; 61:685-693.
45. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993; 329:987-94.
46. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostivc Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014; 12:837-42.
47. Wang WT, Liang JH, Wang Li, et al. The prognostic value of 25-hydroxy vitamin D deficiency and its interaction with c-Myc expression in diffuse large B cell lymphoma. Annals of Hematology.2020; 99:2377-84.
48. Sehn LH, Scott DW, Chhanabhai M, et al. Impact of concordant and disconcordant bone marrow involement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol.2011; 29:1452-7.
49. Ott G, Ziepert M, Klapper W, et al. Immunoblastic morphology but not the immunohistochemical GCB/non GCB classifier predicts outcome in diffuse large B-cell lymphoma in the RİCOVER-60 trial of the DSH-NHL. Blood. 2010; 116:4916-25.
50. Li M, Liu Y, Wang Y, et al. Anaplastic variant of diffuse large B-cell lymphoma displays intricate genetic alterations and distinct histological features. Am J Surg Pathol. 2017; 41:1322-32.
51. Yamaguchi M, Seto M, Okamato M, et al. De novo CD5+ diffuse large B-cell lymphoma: a clinicopathologic study of 109 patients. Blood. 2002; 99:815-21.
52. Xu-Monette ZY, Tu M, Jabbar KJ, et al. Clinical and biological significance of de novo CD5+ diffuse large B-cell lymphoma in Western countries. Oncotarget. 2015; 6:5615-33.
53. Winter JN, Weller EA, Horning SJ, et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. Blood. 2006; 107:4207-13.
54. Sarkozy C, Traverse-Glehen A, Coiffer B. Double- hit and double-protein –expression lymphomas:aggressive and refractory lymphomas. Lancet Oncol. 2015; 16:e555-67.
55. Savage KJ, Slack GW, Mottok A, et al. Impact of dual expresson of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. Blood. 2016; 127:2182-8.
56. Hu S, Xu-Monette ZY, Balasubramanyam A, et al. CD30 expression defines a novel subgroup of dffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature:a report from the International DLBCL Rituximab –CHOP Concortium Program Study. Blood. 121:2715-24.
57. Koh YW, Hwang HS, Park CS, et al. Prognostic effect of Ki-67 expression in rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone-treated diffuse large B-cell lymphoma is limited to non-germinal center B-cell-like in late-elderly patients. Leuk Lymphoma. 2015; 56:2630-6.

58. Obermann EC, Csato M, Dirnnhofer S, et al. Aberrations of the MYC gene in unselected cases of diffuse large B-cell lymphoma are rare and unpredictable by morphological or immunohistochemical assessment. J Clin Pathol.2009; 62:754-6.
59. Lu TX, Fan L, Wang L, et al. MYC or BCL2 copy number aberration is a strong predictor of outcome in patients with diffuse large B-cell lymphoma. Oncotarget. 2015; 6:18374-88.
60. Shustik J, Han G, Farinha P, et al. Correlations between BCL6 rearrangement and outcome in patients with diffuse large B-cell lymphoma treated with CHOP or R-CHOP. Haematologica.2010; 95:96-101.
61. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood. 2009;114: 3533-7.
62. Tzankov A, Xu-Monette ZY, Gerhald M, et al. Rearrangements of MYC gene facilitate risk stratification in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Mod Pathol. 2014; 27:958-71.
63. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations:the critical factors associated with survival. Blood.2009; 114: 2273-9.
64. Pillai RK, Sathanoori M, Van Oss SB, et al. Double-hit B-cell lymphomas with BCL6 and MYC translocations are aggressive, frequently extranodal lymphomas distinct from BCL2 double-hit B-cell lymphomas. Am J Surg Pathol. 2013;37:323-32.
65. Ye Q, Xu-Monette ZY, Tzankov A, et al. Prognostic impact of concurrent MYC and BCL-6 rearrangements and expression in de novo diffuse large B-cell lymphoma. Oncotarget. 2016; 7:2401-16.
66. Ichikawa A, Kinoshita T, Watanabe T, et al. Mutations of the p53 gene as a prognostic factor in aggressive B-cell lymphoma. N Engl J Med. 1997; 337:529-34.
67. Jardin F, Jais JP, Molina TJ, et al. Diffuse large B-cell lymphoma with CDKN2A deletion have a distinct gene expression signature and a poor prognosis under R-CHOP treatment:a GELA study . Blood.2010; 116:1092-104.
68. Trinh DL, Scott DW, Morin RD, et al. Analysis of FOXO1 mutations in diffuse large B-cell lymphoma. Blood. 2013; 121:3666-74.
69. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large B-cell lymphomas. N Engl J Med .2008; 2313-23.
70. Clozel T, Yang S, Elstrom RL, et al. Mechanism-based epigenetic chemosensitization therapy of diffuse large B-cell lymphoma. Cancer Discov. 2013; 3:1002-19.
71. Perry AM, Candesa –Salzman TM, Meyer PN, et al. A new biologic prognostic model based on immunohistochemistry predicts survival in patients with diffuse large B-cell lymphoma. Blood. 2012; 120: 2290-6.
72. Epperla N, Hamadani M. Hematopoetic cell transplantation for diffuse large B-cell and follicular lymphoma:-current controversies and advances. Hematol Oncol Stem Cell Ther. 2017; 10(4):277-284.