

8. BÖLÜM

SANTRAL SİNİR SİSTEMİNİN PRİMER DİFFÜZ BÜYÜK B HÜCRELİ LENFOMASI

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GİRİŞ

Beyin tümörlerinin yaklaşık %4-7'sini primer santral sinir sistemi lenfomaları oluşturmaktadır (1). Primer santral sinir sistemi lenfomalarının yaklaşık %90-95'i diffüz büyük B hücreli lenfomalardır (DBBHL) (2). Primer santral sinir sistemi diffüz büyük B hücreli lenfoma (PSSS DBBHL) beyin, spinal kord, leptomeninks ya da göz lokalizasyonlarında görülen DBBHL'yi kapsar (3). PSSS DBBHL'nin insidansı 0,47/ 100 000'dir (4). Erkeklerde sıklığı daha fazla olmakla birlikte bağışıklık problemi bulunmayan kişilerde görülme yaşı sıklıkla 60 yaşın üzeridir (5, 6). HIV/AIDS'li hastalarda daha erken yaşlarda tanı konmakta olup bu hastalarda PSSS DBBHL'nin median görülme yaşı 40,7 olarak saptanmıştır (7).

ETİYOLOJİ

Primer santral sinir sistemi diffüz büyük B hücreli lenfoma için en önemli risk faktörü konjenital veya edinsel immün yetmezliktir (5). İmmün yetmezliği bulunmayan popülasyonda etiyojisi henüz tam olarak aydınlatılamamıştır. Yapılan çalışmalarda EBV, HHV6, HHV8, poliovirüs ile ilişki saptanamamıştır (8-11). HIV/AIDS, iatrojenik immünsüpresyon ve konjenital

immün yetmezlik sendromlarında primer santral sinir sistemi lenfomalarının görülme riski yaklaşık %4'tür (5).

LOKALİZASYON

Primer santral sinir sistemi diffüz büyük B hücreli lenfoma beyin, spinal kord, leptomeninks ve gözde yerleşim gösteren DBBHL'leri içermektedir (12). Tümörlerin yaklaşık %60'ı supratentorial yerleşimlidir (13). Vakaların %30-40'ı multipl odaklar halinde izlenir (14).

Primer intraoküler DBBHL'ler sıklıkla vitreus sıvısı ve retinada yerleşim gösterir (15). Hastaların yaklaşık % 20'si intraoküler lezyonlar ile başvurur; intraoküler DBBHL'li olgularda %90'a ulaşan oranda kontralateral tümör varlığı ve kranial sinir sisteminin parankimal tutulumu görülmür (3).

PSSS DBBHL'lerde %5 oranında leptomeninks tutulumu görülürken merkezi sinir sisteminin sekonder lenfomaları sıklıkla dura ve leptomeninkse uzanım göstermekte; intraoküler tutulumlarda koroid yerleşimi beklenmektedir (13, 16).

Primer beyin lenfomalarında nüksler %90-95 oranında beyin ile sınırlıdır. Tümörün sistemik yayılımı nadiren görülebilmektedir (3, 17-20).

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lenfoma, NOS'tan ayırmak gerekir (33, 72). Yüksek dereceli B hücreli lenfoma, NOS, morfolojik, immünofenotipik ve genetik özellikleri DBBHL ve Burkitt lenfomaya benzeyen heterojen bir matür B hücre lenfoması grubudur (3). MYC gen rearranjmanları görülebilse de hem MYC ve BCL2 ve / veya BCL6 rearranjmanları negatiftir (3). Neoplastik hücreler blastoid morfolojili ve büyük olarak izlenir (3). Morfolojik olarak tingible body makrofajlar, dağınık mitotik figürler ve apoptotik kalıntılar içeren monomorfik hücre tabakaları görülebilse de Burkitt lenfoma ile uyumsuz olan immünohistokimya ve moleküler genetik bulgular gösterirler (3). Blastoid morfolojili olgularda ayrıca B-lenfoblastik lenfoma / lösemi (TdT ve / veya CD34 pozitif) ve mantle hücreli lenfomanın blastoid varyantı (Bcl-1 / siklin D1 pozitif ve / veya SOX11) da ekarte edilmelidir (12).

Glioblastomlarda görülen coğrafik nekrozlar PSSS DBBHL'lerde görülebilir. Ancak PSSS DBBHL'lerde mikrovasküler proliferasyon ve psödo-palizatlaşma görülmez. Tümör hücreleri sitolojik olarak sıklıkla glioblastom hücrelerinden daha büyük ve daha yuvarlaktır, pleomorfizm daha azdır (48).

İntravasküler büyük B hücreli lenfomada, küçük kan damarları (özellikle kapiller) lümeninde izlenen neoplastik hücreler görülür. Damar dışında infiltrasyon nadirdir (48).

ALK+ anaplastik büyük hücreli lenfoma klinik olarak enfeksiyöz hastalıkları taklit eder. Beyin parankiminin yanı sıra %75 olguda leptomeninks ve dura tutulumu gösterir. Hallmark hücreleri izlenir. İmmünohistokimyasal olarak T antijenleri ve CD30, ALK pozitifliği beklenir (48).

HIV enfeksiyonu ilişkili DBBHL'li olgularda CD4+ T hücre oranı çok düşük izlenir. Sıklıkla immünoblastik morfoloji hakimdir. EBV olguların tamamı yakınında pozitifdir (48).

KAYNAKLAR

1. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG. Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990-1994. *Neuro Oncol.* 1999;1(1):14-25. DOI: 10.1093/neuonc/1.1.14.
2. Dandachi D, Ostrom QT, Chong I, Serpa JA, Giordano TP, Kruchko C, et al. Primary central nervous system lymphoma in patients with and without HIV infection: a multicenter study and comparison with U.S national data. *Cancer Causes Control.* 2019;30(5):477-88. DOI: 10.1007/s10552-019-01144-8.
3. Kluin PM, Deckert M, Ferry JA. 2017 Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editor. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* p. 300-2. Lyon: International Agency for Research on Cancer.
4. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer.* 2011;105(9):1414-8. DOI: 10.1038/bjc.2011.357.
5. O'Neill BP, Decker PA, Tieu C, Cerhan JR. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol.* 2013;88(12):997-1000. DOI: 10.1002/ajh.23551.
6. Cote TR, Manns A, Hardy CR, Yellin FJ, Hartge P. Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. AIDS/Cancer Study Group. *J Natl Cancer Inst.* 1996;88(10):675-9.
7. Gopal S, Patel MR, Yanik EL, Cole SR, Achenbach CJ, Napravnik S, et al. Temporal trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. *J Natl Cancer Inst.* 2013;105(16):1221-9.
8. Montesinos-Rongen M, Besleaga R, Heinsohn S, Siebert R, Kabisch H, Wiestler OD, et al. Absence of simian virus 40 DNA sequences in primary central nervous system lymphoma in HIV-negative patients. *Virchows Arch.* 2004;444(5):436-8.
9. Montesinos-Rongen M, Hans VH, Eis-Hubinger AM, Prinz M, Schaller C, Van Roost D, et al. Human herpes virus-8 is not associated with primary central nervous system lymphoma in HIV-negative patients. *Acta Neuropathol.* 2001;102(5):489-95.
10. Murray JM, Morgello S. Polyomaviruses and primary central nervous system lymphomas. *Neurology.* 2004;63(7):1299-301.
11. Paulus W, Jellinger K, Hallas C, Ott G, Muller-Hermelink HK. Human herpesvirus-6 and Epstein-Barr virus genome in primary cerebral lymphomas. *Neurology.* 1993;43(8):1591-3.
12. Lauw MIS, Lucas CG, Ohgami RS, Wen KW. Primary Central Nervous System Lymphomas: A Diagnostic Overview of Key Histomorphologic, Immunophenotypic, and Genetic Features. *Diagnostics (Basel).* 2020;10(12).
13. Kluin PM, Deckert M, Ferry JA. 2008 Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editor. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* p. 240-1. Lyon: International Agency for Research on Cancer.

14. Deckert M, Engert A, Bruck W, Ferreri AJ, Finke J, Illerhaus G, et al. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. *Leukemia*. 2011;25(12):1797-807.
15. Giannini C, Dogan A, Salomao DR. CNS lymphoma: a practical diagnostic approach. *J Neuropathol Exp Neurol*. 2014;73(6):478-94.
16. Green K, Hogg JP. 2020 Central Nervous System Lymphoma. In: editor.^editors. ed. StatPearls. p. Treasure Island (FL).
17. Booman M, Douwes J, Legdeur MC, van Baarlen J, Schuurin E, Kluin P. From brain to testis: immune escape and clonal selection in a B cell lymphoma with selective outgrowth in two immune sanctuaries [correction of sanctuaries]. *Haematologica*. 2007;92(6):e69-71.
18. Harney J, Pope A, Short SC. Primary central nervous system lymphoma with testicular relapse. *Clin Oncol (R Coll Radiol)*. 2004;16(3):193-5.
19. Jahnke K, Thiel E, Martus P, Herrlinger U, Weller M, Fischer L, et al. Relapse of primary central nervous system lymphoma: clinical features, outcome and prognostic factors. *J Neurooncol*. 2006;80(2):159-65.
20. Rajappa SJ, Uppin SG, Digumarti R. Testicular relapse of primary central nervous system lymphoma. *Leuk Lymphoma*. 2007;48(5):1023-5.
21. Batchelor T, Loeffler JS. Primary CNS lymphoma. *J Clin Oncol*. 2006;24(8):1281-8.
22. Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. *Nat Rev Neurol*. 2013;9(6):317-27.
23. Pels H, Schlegel U. Primary central nervous system lymphoma. *Curr Treat Options Neurol*. 2006;8(4):346-57.
24. Kuker W, Nagele T, Korfel A, Heckl S, Thiel E, Bamberg M, et al. Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *J Neurooncol*. 2005;72(2):169-77.
25. Bruck W, Brunn A, Klapper W, Kuhlmann T, Metz I, Paulus W, et al. [Differential diagnosis of lymphoid infiltrates in the central nervous system: experience of the Network Lymphomas and Lymphomatoid Lesions in the Nervous System]. *Pathologe*. 2013;34(3):186-97.
26. Ponzoni M, Berger F, Chassagne-Clement C, Tinguely M, Jouvett A, Ferreri AJ, et al. Reactive perivascular T-cell infiltrate predicts survival in primary central nervous system B-cell lymphomas. *Br J Haematol*. 2007;138(3):316-23.
27. Camilleri-Broet S, Criniere E, Broet P, Delwail V, Mokhtari K, Moreau A, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood*. 2006;107(1):190-6.
28. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-82.
29. Hattab EM, Martin SE, Al-Khatib SM, Kupsky WJ, Vance GH, Stohler RA, et al. Most primary central nervous system diffuse large B-cell lymphomas occurring in immunocompetent individuals belong to the nongerminal center subtype: a retrospective analysis of 31 cases. *Mod Pathol*. 2010;23(2):235-43.
30. Lin CH, Kuo KT, Chuang SS, Kuo SH, Chang JH, Chang KC, et al. Comparison of the expression and prognostic significance of differentiation markers between diffuse large B-cell lymphoma of central nervous system origin and peripheral nodal origin. *Clin Cancer Res*. 2006;12(4):1152-6.
31. Makino K, Nakamura H, Shinojima N, Kuroda JI, Yano S, Mikami Y, et al. BCL2 expression is associated with a poor prognosis independent of cellular origin in primary central nervous system diffuse large B-cell lymphoma. *J Neurooncol*. 2018;140(1):115-21.
32. King RL, Goodlad JR, Calaminici M, Dotlic S, Montes-Moreno S, Oschlies I, et al. Lymphomas arising in immune-privileged sites: insights into biology, diagnosis, and pathogenesis. *Virchows Arch*. 2020;476(5):647-65.
33. Brunn A, Nagel I, Montesinos-Rongen M, Klapper W, Vater I, Paulus W, et al. Frequent triple-hit expression of MYC, BCL2, and BCL6 in primary lymphoma of the central nervous system and absence of a favorable MYC(low)BCL2 (low) subgroup may underlie the inferior prognosis as compared to systemic diffuse large B cell lymphomas. *Acta Neuropathol*. 2013;126(4):603-5.
34. Montesinos-Rongen M, Schafer E, Siebert R, Deckert M. Genes regulating the B cell receptor pathway are recurrently mutated in primary central nervous system lymphoma. *Acta Neuropathol*. 2012;124(6):905-6.
35. Gill KZ, Iwamoto F, Allen A, Hoehn D, Murty VV, Alobeid B, et al. MYC protein expression in primary diffuse large B-cell lymphoma of the central nervous system. *PLoS One*. 2014;9(12):e114398.
36. Kim S, Nam SJ, Kwon D, Kim H, Lee E, Kim TM, et al. MYC and BCL2 overexpression is associated with a higher class of Memorial Sloan-Kettering Cancer Center prognostic model and poor clinical outcome in primary diffuse large B-cell lymphoma of the central nervous system. *BMC Cancer*. 2016;16:363.
37. Shi QY, Feng X, Bao W, Ma J, Lv JH, Wang X, et al. MYC/BCL2 Co-Expression Is a Stronger Prognostic Factor Compared With the Cell-of-Origin Classification in Primary CNS DLBCL. *J Neuropathol Exp Neurol*. 2017;76(11):942-8.
38. Tapia G, Baptista MJ, Munoz-Marmol AM, Gaafar A, Puente-Pomposo M, Garcia O, et al. MYC protein expression is associated with poor prognosis in primary diffuse large B-cell lymphoma of the central nervous system. *APMIS*. 2015;123(7):596-603.
39. Guo S, Bai Q, Rohr J, Wang Y, Liu Y, Zeng K, et al. Clinicopathological features of primary diffuse large B-cell lymphoma of the central nervous system - strong EZH2 expression implying diagnostic and therapeutic implication. *APMIS*. 2016;124(12):1054-62.
40. Liu J, Wang Y, Liu Y, Liu Z, Cui Q, Ji N, et al. Immunohistochemical profile and prognostic significance in primary central nervous system lymphoma: Analysis of 89 cases. *Oncol Lett*. 2017;14(5):5505-12.
41. Booman M, Douwes J, Glas AM, Riemersma SA, Jordanova ES, Kok K, et al. Mechanisms and effects of loss

- of human leukocyte antigen class II expression in immune-privileged site-associated B-cell lymphoma. *Clin Cancer Res.* 2006;12(9):2698-705.
42. Riemersma SA, Oudejans JJ, Vonk MJ, Dreef EJ, Prins FA, Jansen PM, et al. High numbers of tumour-infiltrating activated cytotoxic T lymphocytes, and frequent loss of HLA class I and II expression, are features of aggressive B cell lymphomas of the brain and testis. *J Pathol.* 2005;206(3):328-36.
 43. Riemersma SA, Jordanova ES, Schop RF, Philippo K, Looijenga LH, Schuurin E, et al. Extensive genetic alterations of the HLA region, including homozygous deletions of HLA class II genes in B-cell lymphomas arising in immune-privileged sites. *Blood.* 2000;96(10):3569-77.
 44. Bhagavathi S, Sharathkumar A, Hunter S, Sung L, Kanhere R, Venturina MD, et al. Activated B-cell immunophenotype might be associated with poor prognosis of primary central nervous system lymphomas. *Clin Neuropathol.* 2008;27(1):13-20.
 45. Feuerhake F, Baumer C, Cyron D, Illerhaus G, Olshewski M, Tilgner J, et al. Primary CNS lymphoma in immunocompetent patients from 1989 to 2001: a retrospective analysis of 164 cases uniformly diagnosed by stereotactic biopsy. *Acta Neurochir (Wien).* 2006;148(8):831-8; discussion 8.
 46. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol.* 2006;24(28):4570-4.
 47. Montesinos-Rongen M, Siebert R, Deckert M. Primary lymphoma of the central nervous system: just DLBCL or not? *Blood.* 2009;113(1):7-10.
 48. Medeiros LJ, Muzzafar T, Miranda RN. 2018 Primary diffuse large B-cell lymphoma of central nervous system. In: Medeiros LJ, Miranda RM, editor. *^editors. 2 ed. Diagnostic Pathology Lymph Nodes and Extranodal Lymphomas.* p. 476-85. Philadelphia: Elsevier.
 49. Lossos C, Bayraktar S, Weinzierl E, Younes SF, Hosein PJ, Tibshirani RJ, et al. LMO2 and BCL6 are associated with improved survival in primary central nervous system lymphoma. *Br J Haematol.* 2014;165(5):640-8.
 50. Momota H, Narita Y, Maeshima AM, Miyakita Y, Shinomiya A, Maruyama T, et al. Prognostic value of immunohistochemical profile and response to high-dose methotrexate therapy in primary CNS lymphoma. *J Neurooncol.* 2010;98(3):341-8.
 51. Preusser M, Woehrer A, Koperek O, Rottenfusser A, Dieckmann K, Gatterbauer B, et al. Primary central nervous system lymphoma: a clinicopathological study of 75 cases. *Pathology.* 2010;42(6):547-52.
 52. Raoux D, Duband S, Forest F, Trombert B, Chambonniere ML, Dumollard JM, et al. Primary central nervous system lymphoma: immunohistochemical profile and prognostic significance. *Neuropathology.* 2010;30(3):232-40.
 53. Song MK, Chung JS, Joo YD, Lee SM, Oh SY, Shin DH, et al. Clinical importance of Bcl-6-positive non-deep-site involvement in non-HIV-related primary central nervous system diffuse large B-cell lymphoma. *J Neurooncol.* 2011;104(3):825-31.
 54. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol.* 1998;16(3):859-63.
 55. Cady FM, O'Neill BP, Law ME, Decker PA, Kurtz DM, Giannini C, et al. Del(6)(q22) and BCL6 rearrangements in primary CNS lymphoma are indicators of an aggressive clinical course. *J Clin Oncol.* 2008;26(29):4814-9.
 56. Gonzalez-Aguilar A, Idbaih A, Boisselier B, Habbita N, Rossetto M, Laurence A, et al. Recurrent mutations of MYD88 and TBL1XR1 in primary central nervous system lymphomas. *Clin Cancer Res.* 2012;18(19):5203-11.
 57. Bhagavathi S, Wilson JD. Primary central nervous system lymphoma. *Arch Pathol Lab Med.* 2008;132(11):1830-4.
 58. Basso K, Dalla-Favera R. BCL6: master regulator of the germinal center reaction and key oncogene in B cell lymphomagenesis. *Adv Immunol.* 2010;105:193-210.
 59. Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol.* 2013;31(25):3061-8.
 60. Braaten KM, Betensky RA, de Leval L, Okada Y, Hochberg FH, Louis DN, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. *Clin Cancer Res.* 2003;9(3):1063-9.
 61. Kreher S, Johrens K, Strehlow F, Martus P, Borowiec K, Radke J, et al. Prognostic impact of B-cell lymphoma 6 in primary CNS lymphoma. *Neuro Oncol.* 2015;17(7):1016-21.
 62. Levy O, Deangelis LM, Filippa DA, Panageas KS, Abrey LE. Bcl-6 predicts improved prognosis in primary central nervous system lymphoma. *Cancer.* 2008;112(1):151-6.
 63. Montesinos-Rongen M, Godlewska E, Brunn A, Wiestler OD, Siebert R, Deckert M. Activating L265P mutations of the MYD88 gene are common in primary central nervous system lymphoma. *Acta Neuropathol.* 2011;122(6):791-2.
 64. Montesinos-Rongen M, Zuhlke-Jenisch R, Gesk S, Martin-Subero JL, Schaller C, Van Roost D, et al. Interphase cytogenetic analysis of lymphoma-associated chromosomal breakpoints in primary diffuse large B-cell lymphomas of the central nervous system. *J Neuropathol Exp Neurol.* 2002;61(10):926-33.
 65. Schwindt H, Vater I, Kreuz M, Montesinos-Rongen M, Brunn A, Richter J, et al. Chromosomal imbalances and partial uniparental disomies in primary central nervous system lymphoma. *Leukemia.* 2009;23(10):1875-84.
 66. Vater I, Montesinos-Rongen M, Schlesner M, Haake A, Purschke F, Sprute R, et al. The mutational pattern of primary lymphoma of the central nervous system determined by whole-exome sequencing. *Leukemia.* 2015;29(3):677-85.
 67. Bruno A, Boisselier B, Labreche K, Marie Y, Polivka M, Jouvet A, et al. Mutational analysis of primary central nervous system lymphoma. *Oncotarget.* 2014;5(13):5065-75.

68. Braggio E, Van Wier S, Ojha J, McPhail E, Asmann YW, Egan J, et al. Genome-Wide Analysis Uncovers Novel Recurrent Alterations in Primary Central Nervous System Lymphomas. *Clin Cancer Res.* 2015;21(17):3986-94.
69. Hattori K, Sakata-Yanagimoto M, Okoshi Y, Goshima Y, Yanagimoto S, Nakamoto-Matsubara R, et al. MYD88 (L265P) mutation is associated with an unfavourable outcome of primary central nervous system lymphoma. *Br J Haematol.* 2017;177(3):492-4.
70. Todorovic Balint M, Jelacic J, Mihaljevic B, Kostic J, Stanic B, Balint B, et al. Gene Mutation Profiles in Primary Diffuse Large B Cell Lymphoma of Central Nervous System: Next Generation Sequencing Analyses. *Int J Mol Sci.* 2016;17(5).
71. Cai Q, Fang Y, Young KH. Primary Central Nervous System Lymphoma: Molecular Pathogenesis and Advances in Treatment. *Transl Oncol.* 2019;12(3):523-38.
72. Fukumura K, Kawazu M, Kojima S, Ueno T, Sai E, Soda M, et al. Genomic characterization of primary central nervous system lymphoma. *Acta Neuropathol.* 2016;131(6):865-75.
73. Wang JQ, Jeelall YS, Ferguson LL, Horikawa K. Toll-Like Receptors and Cancer: MYD88 Mutation and Inflammation. *Front Immunol.* 2014;5:367.
74. Yu X, Li W, Deng Q, Li L, Hsi ED, Young KH, et al. MYD88 L265P Mutation in Lymphoid Malignancies. *Cancer Res.* 2018;78(10):2457-62.
75. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature.* 2011;470(7332):115-9.
76. Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Ro-messer PB, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature.* 2010;463(7277):88-92.
77. Chu LC, Eberhart CG, Grossman SA, Herman JG. Epigenetic silencing of multiple genes in primary CNS lymphoma. *Int J Cancer.* 2006;119(10):2487-91.
78. Mrugala MM, Rubenstein JL, Ponzoni M, Batchelor TT. Insights into the biology of primary central nervous system lymphoma. *Curr Oncol Rep.* 2009;11(1):73-80.
79. Adachi J, Mishima K, Wakiya K, Suzuki T, Fukuoka K, Yanagisawa T, et al. O(6)-methylguanine-DNA methyltransferase promoter methylation in 45 primary central nervous system lymphomas: quantitative assessment of methylation and response to temozolomide treatment. *J Neurooncol.* 2012;107(1):147-53.
80. Kurzwelly D, Glas M, Roth P, Weimann E, Lohner H, Waha A, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. *J Neurooncol.* 2010;97(3):389-92.
81. Toffolatti L, Scquizzato E, Cavallin S, Canal F, Scarpa M, Stefani PM, et al. MGMT promoter methylation and correlation with protein expression in primary central nervous system lymphoma. *Virchows Arch.* 2014;465(5):579-86.