Reunión de la territorial Asturiana de la SEAP.
5 y 6 de Octubre de 2012.

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UPDATE IN B-CELL NON HODGKIN LYMPHOMAS. NEW DIAGNOSTIC AND PROGNOSTIC MOLECULAR MARKERS.

ACTUALIZACION EN LINFOMAS B MADUROS. NUEVOS MARCADORES DIAGNÓSTICOS Y PRONÓSTICOS.

1. MATURE AGRESSIVE B CELL LYMPHOMAS

Mature agressive B cell lymphomas include Burkitt Lymphoma, Diffuse Large B cell lymphoma and its variants, B cell lymphoma with features intermediate between Burkitt Lymphoma and Diffuse Large B cell Lymphoma, EBV positive Diffuse Large B cell lymphoma of the elderly, Plasmablastic Lymphoma and related lymphomas (Large B cell Lymphomas with plasmablastic features).

BURKITT LYMPHOMA

Burkitt lymphoma is an aggressive B –cell lymphoma of very short doubling-time that frequently develops in extranodal sites (jaw, ileocecal region, CNS and bone marrow). It is the most common lymphoma in children (30-50%) and is rare in adults (1-2% of adult lymphomas). 3 clinical variants are recognized (endemic, sporadic and immunodeficiency associated)[1] with variable associations with EBV positivity. Translocations involving C-MYC oncogene are required for the diagnosis although are not specific for BL (being found in DLBCL, B cell lymphoma with features intermediate between BL and DLBCl and Plasmablastic Lymphoma, among others) [1-5].

Morphologically BL is characterized by a monomorphic, medium-sized cell proliferation with a cohesive pattern of growth. A starry sky pattern is

characteristic but can also be found in conventional DLBCL. The nuclei of the cells are round with finely clumped chromatin and inconspicuous nucleoli or multiple small paracentral nucleoli. The immunophenotype is defined by high expression of CD20, surface IgM but not IgD and homogeneous expression of CD10, BCL6 and absence of BCL2 and TdT[1, 6]. Aditional markers can be used, being TCL1 positive, cD44 negative[7] and MUM1 commonly negative. Recently available, C-MYC nuclear expression[8] and v-PREBB3 immunostainings[9] can be used in the diagnostic panel. Proliferation index as measured using Ki67 is very close to 100%. The single immunophenotypic exception that is accepted in an otherwise typical BL is the weak or partial expression of BCL2[1].

Genetically BL is characterized by a simple karyotype with C-MYC translocations (detected in almost all cases using 8q24 break-apart FISH assays). The absence of C-MYC break using BA probes should make consider an alternative diagnosis. [10, 11]

BL is a potentially curable disease, particularly the endemic and sporadic variants After treatment with “high-intensity, short duration” combination chemotherapy, cure rates achieve 80-90% even in patients with disseminated disease. Poor prognosis markers are CNS and bone marrow involvement, unresectable tumor masses >10 cm and high serum LDH.

B CELL LYMPHOMA WITH FEATURES INTERMEDIATE BETWEEN BURKITT LYMPHOMA AND DIFFUSE LARGE B CELL LYMPHOMA.

This category includes cases that do not exhibit the well defined features of Burkitt lymphoma but are also atypical for Diffuse large B cell lymphoma. This category is, by the moment, a specific entity but a heterogeneous group of aggressive lymphomas previously recognized as atypical Burkitt Lymphoma or Burkitt-like lymphoma.

Within this group of cases, double hit lymphomas are the best characterized subgroup and are defined by the concurrent IGH-BCL2/t(14;18)(q32;q21) and MYC/8q24 rearrangements (rarely 3q27/BCL6 is involved). These lymphomas have heterogeneous morphological features (Burkitt-like, atypical BL, DLBCL, blastoid FL), germinal center immunophenotype and dismal outcome[12, 13]. Features that suggest this diagnosis include BL-like morphology together with

strong BCL2 expression or blastoid morphology in a case with previous FL.

DIFFUSE LARGE B CELL LYMPHOMA WITH C-MYC TRANSLOCATIONS.

Conventional DLBCL cases can have very high proliferation rate as measured with Ki67 and a starry sky pattern, CD10 overexpression and C-MYC (single) rearrangement in up to 15% of the cases[2, 3]. These cases have commonly a Germinal Center B profile and worse outcome and higher shorter time to CNS relapse than C-MYC negative DLBCL and probably require intensive treatment regimens different than conventional R-CHOP.

DIFFUSE LARGE B CELL LYMPHOMA NOS. CELL OF ORIGIN CLASSIFICATION.

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of NHL in adults, accounting for more than 80% of aggressive lymphomas[1]. DLBCL is a heterogeneous group of tumors with different genetic abnormalities, clinical features, response to treatment and prognosis[14]. This heterogeneity hinders outcome prediction based on clinical and/or molecular parameters.

Biological heterogeneity of DLBCL has been shown substantially to reflect the cell origin of these tumors from germinal center (GCB) or activated B-cells (ABC). Notably, these differences were significant independently of IPI stratification, showing that identifying cell or origin signatures captures features other than IPI and can refine outcome prediction[15]. These differences between GCB and ABC DLBCL remain significant in patients treated with combined immunochemotherapy including Rituximab[16].

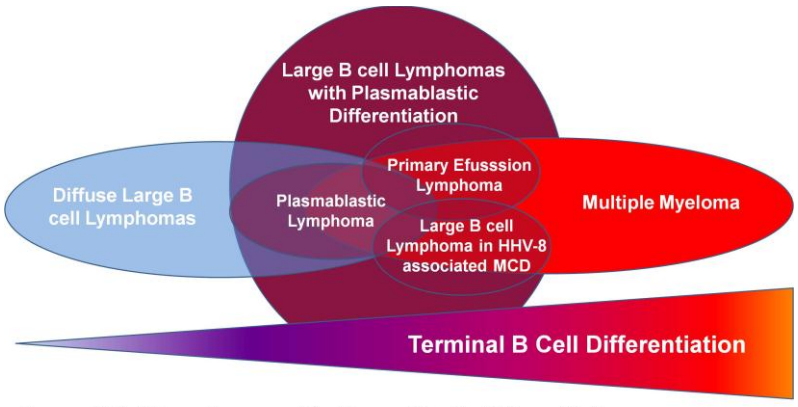
Immunostaining approaches allow to classify these entities in GCB or ABC/non-GCB subgroups(5-7) and have been proposed as feasible surrogates of GEP. Increasing rates of correlation between GEP and immunohistochemical profiles has been obtained with the development of expanded panels of antibodies[17-21], although there is still a need of optimizing the reproducibility among different laboratories in performing and scoring the immunohistochemical studies before incorporating in the routine practice to optimize treatment decisions[22, 23].

LARGE B CELL LYMPHOMAS WITH PLASMABLASTIC DIFFERENTIATION.

Plasmablastic differentiation can be found in a variety of Large B Cell Lymphomas, including Plasmablastic Lymphoma[1, 24], ALK-Positive Large B Cell Lymphoma[25, 26], Primary Effusion Lymphoma[27], Large B Cell Lymphoma arising in HHV-8-associated Multicentric Castleman Disease[28, 29] and Diffuse Large B Cell Lymphoma with partial plasmablastic phenotype/DLBCL with immunoblastic differentiation[30]. These tumors are characterized by the acquisition of the transcriptional profile of plasma cells (with overexpression of PRDM1/Blimp1 and XBP1s, in concert with the extinction of the B cell differentiation program) by proliferating immunoblasts. Large B Cell Lymphoma with Plasmablastic Differentiation, is almost always associated with an aggressive clinical behavior[31].

The diagnostic borders with conventional DLBCL and Multiple Myeloma are ill defined and multiple adverse molecular events have been recently described that can be used as diagnostic tools (Blimp1 expression[32], C-MYC[4, 5] and ALK translocations[25, 26, 33] among others) (Figure 1)

FIGURE 1



Large B Cell Lymphomas with Plasmablastic Differentiation.

Plasmablastic Lymphoma.
ALK-positive large B-cell lymphoma.
Primary Efussion Lymphoma PEL (cavitary or extracavitary).
Large B cell Lymphoma arising in HHV-8 associated Multicentric Castleman Disease.
Diffuse Large B cell Lymphomas with partial plasmablastic phenotype/DLBCL with immunoblastic differentiation.

EBV POSITIVE DIFFUSE LARGE B CELL LYMPHOMA OF THE ELDERLY.

EBV-positive diffuse large B cell lymphoma of the elderly is a diffuse large B cell lymphoma subtype[34] that has recently been recognized as a provisional entity among the diffuse large B cell lymphoma subtypes within the WHO classification. It is defined as a clonal B cell lymphoid proliferation that occurs in patients older than 50 years without any known immunodeficiency or previous lymphoma. Cases of lymphomatoid granulomatosis, infectious mononucleosis or other well defined disorders (such as plasmablastic lymphoma, primary effusion lymphoma and diffuse large B cell lymphoma associated with chronic inflammation) that may be EBV-positive are excluded from this category[35].

This subtype of diffuse large B cell lymphoma was initially reported as “senile EBV-associated B-cell lymphoproliferative disorder” [36]. In recent years, it has been noted that defective immune surveillance for EBV may develop late in life and be associated with the development of EBV-positive B cell ymphoproliferative disorder in individuals who otherwise have no apparent immune deficiency[34]. Currently, age-related EBV-positive lymphoproliferative disorder accounts for 8-10% of diffuse large B cell lymphoma cases among East Asian patients with no predisposing immunodeficiency. The largest western series published to date[37] demonstrates that the spectrum of EBV related lesions in western populations is wider than previously expected and mirrors the situation found in Asian countries. Additionally a direct comparison between the prevalence of this particular neoplasm between Mexican and German populations demonstrates that EBV-positive diffuse large B-cell lymphoma of the elderly in a Latin-American (Mexican) population has a similar prevalence, comparable with what has been reported in Asian countries, and in contrast to the low frequency in Western populations (1-3%)[38]. Recent data demonstrate that EBV-positive diffuse large B cell lymphoma of the elderly is an agressive clonal B cell neoplasm with frequent activated phenotype (ABC) that is associated with activation of both classical and alternative Nuclear Factor-kB pathways[39]. Morphological features (with polymorphic diffuse large B-cell lymphoma, Hodgkin-like and polymorphic lymphoproliferative disorder-like

patterns) are helpful for raising suspicion of a diagnosis that can be confirmed after demonstrating EBV infection and a characteristic phenotype.

2. EARLY B CELL LYMPHOMA. SO CALLED "IN SITU" LESIONS: FOLLICULAR LYMPHOMA IN SITU, MANTLE CELL LYMPHOMA IN SITU AND TISSUE BASED COUNTERPARTS OF B CELL MONOCLONAL LYMPHOCYTOSIS.

   Linfoma B en fase temprana. Lesiones denominadas in situ: Linfoma B Folicular in situ, Linfoma B del manto in situ, Linfocitosis B monoclonal y su contrapartida tisular.

FOLLICULAR LYMPHOMA IN SITU

In situ localization of follicular lymphoma (FL) was described in 2002[40] as being one of the early events associated with FL development, and renamed in the 2008 version of the World Health Organization lymphoma classification as 'intrafollicular neoplasia／in situ follicular lymphoma'[1] It is characterized by the presence of scattered germinal centres that strongly express Bcl-2 protein (coupled with BCL2 traslocation) and germinal center markers (CD10 & Bcl-6), while most of the remaining lymph node shows a pattern of follicular hyperplasia, in absence of interfollicular infiltration. The main differential diagnosis is partial involvement of the lymph node by follicular lymphoma, a situation linked to limited (clinical) stage follicular lymphoma[41]. It is of paramount importance to distinguish both lesions since FL in situ has a very low rate of progression to clinically significant FL while partial involvement by FL are at greater risk for a subsequent FL diagnosis and may already represent overt lymphoma[42]. The risk of progression of the lesions of in situ FL is now being recognized very low; roughly, in 50% of the cases the patients will never develop overt lymphoma, being considered in situ FL an incidental finding[42, 43]. In some patients, however, overt FL is discovered after staging and, interestingly, there is a significant proportion of cases that are discovered to carry a composite lymphoma, other than FL, including Diffuse Large B cell Lymphoma, Splenic Marginal Zone B cell Lymphoma, Chronic Lymphocytic Leukemia, Lymphoplasmacytic Lymphoma and Nodal Marginal Zone

Lymphoma[40, 42, 43]. Few reports, however have been able to identify clear cut clonal identity between bot in situ FL and the overt FL component[44].Thus, in accordance with its early nature, in situ FL is considered, in most instances, to represent tissue infiltration of circulating antigen-experienced, clonal expansions of B cells carrying the t(14;18) translocation commonly detected in healthy persons, termed FL-like B cells[45, 46].

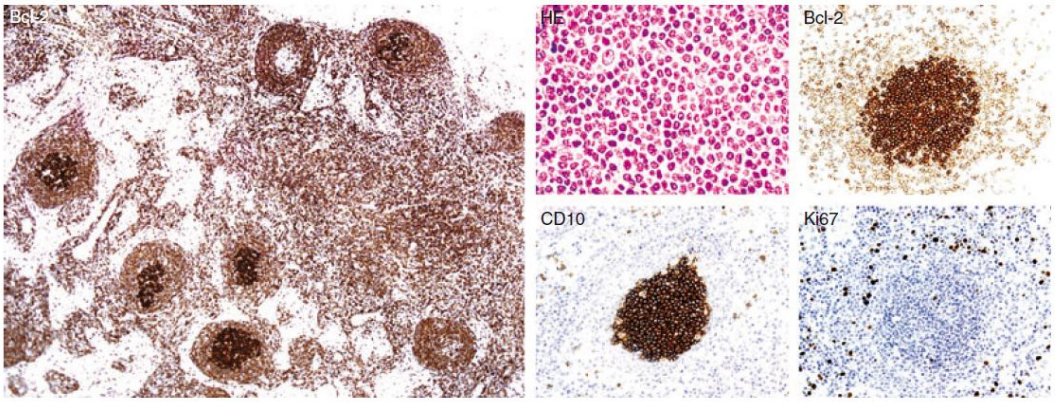


FIGURE 2: Characteristic immunoarquitectural and morphological features of so called “in situ Folllicular Lymphoma”.

MANTLE CELL LYMPHOMA IN SITU

In situ MCL is defined as the presence of cyclinD1 positive cells (usually coupled with t11;14)) in a restricted location in the inner mantle zone of a reactive lymph node[45, 47]. The finding is usually incidental and most of the patients with this condition have never developed a clinically significant neoplasm after several years of follow-up even without treatment[47-49]. The major differential diagnosis is with mantle zone pattern infiltration of the lymph node by overt mantle cell lymphoma, This differential diagnosis is based on immunoarquitectural features including the expansion and replacement of the mantle zone and interfollicular presence of cyclinD1 positive cells in the case of mantle zone pattern MCL. Of note, and similar to the case of t(14;18), persisting circulating clones carrying the t(11;14) may be detected in healthy persons, without any evidence of progression[50]. These findings highlight the low malignant potential of the in situ MCL lesions.

In view of the uncertain clinical behavior of both, FL in situ and MCL in situ, the terminology of FL- or MCL-like B cells of uncertain significance, in parallel with MGUS, was suggested for these tissue-based early lesions at the recent EAHP/SH meeting in Uppsala, Sweden[45].

TISSUE BASED COUNTERPARTS OF B CELL MONOCLONAL LYMPHOCYTOSIS.

Monoclonal B cell Lymphocytosis (MBL) is being increasingly recognized as a potential precursor of CLL[45, 51] and, less frequently other leukemic lymphoid neoplasms. The use of highly sensitive detection methods is able to identify up to 12% of the general population with this condition[52]. However, and in concordance with other early lesions, the rate of progression of MBL to overt CLL is less than 2% per year[53]. Equivalent to MBL, a peripheral blood-based early Chronic Lymphocytic Leukemia, tissue based early Small Lymphocytic Lymphoma is being recognized[54]. The histopathology of these lesions is poorly characterized but a common feature is the presence of interfollicular/parafollicular infiltrates of B cells with a CLL/SLL phenotype (CD20lowCD23+CD5+) without significant arquitectural effacement. Tissue lesion with arquitectural effacement, the presence of clear cut pseudo-follicles and large lymph nodes (>1.5 cm) represent features associated with a higher risk of progression to overt CLL/SLL or the need of treatment. Cases without these “risk” features are proposed to be designated as tissue involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma-like cells of uncertain significance[54] trying to avoid unnecessary treatment to very low risk patients.

REFERENCES

1. Swerdlow SH CE HN, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.*, 2008.

2. 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(20):3360-5.

3. 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(17):3533-7.

4. Taddesse-Heath L, Meloni-Ehrig A, Scheerle J, Kelly JC, Jaffe ES. Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features. *Mod Pathol* 2010; 23(7):991-9.

5. Valera A, Balagué O, Colomo L*, et al.* IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas. *Am J Surg Pathol* 2010; 34(11):1686-94.

6. Haralambieva E, Boerma EJ, van Imhoff GW*, et al.* Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma. *Am J Surg Pathol* 2005; 29(8):1086-94.

7. Rodig SJ, Vergilio JA, Shahsafaei A, Dorfman DM. Characteristic expression patterns of TCL1, CD38, and CD44 identify aggressive lymphomas harboring a MYC translocation. *Am J Surg Pathol* 2008; 32(1):113-22.

8. Ruzinova MB, Caron T, Rodig SJ. Altered subcellular localization of c-Myc protein identifies aggressive B-cell lymphomas harboring a c-MYC translocation. *Am J Surg Pathol* 2010; 34(6):882-91.

9. Rodig SJ, Kutok JL, Paterson JC*, et al.* The pre-B-cell receptor associated protein VpreB3 is a useful diagnostic marker for identifying c-MYC translocated lymphomas. *Haematologica-the Hematology Journal* 2010; 95(12):2056-62.

10. Hummel M, Bentink S, Berger H*, et al.* A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. *N Engl J Med* 2006; 354(23):2419-30.

11. Dave SS, Fu K, Wright GW*, et al.* Molecular diagnosis of Burkitt's lymphoma. *N Engl J Med* 2006; 354(23):2431-42.

12. Li S, Lin P, Fayad LE*, et al.* B-cell lymphomas with MYC/8q24 rearrangements and IGH@BCL2/t(14;18)(q32;q21): an aggressive disease with heterogeneous histology, germinal center B-cell immunophenotype and poor outcome. *Mod Pathol* 2012; 25(1):145-56.

13. Snuderl M, Kolman OK, Chen YB*, et al.* B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. *Am J Surg Pathol* 2010; 34(3):327-40.

14. Lossos IS, Morgensztern D. Prognostic biomarkers in diffuse large B-cell lymphoma. *J Clin Oncol* 2006; 24(6):995-1007.

15. Alizadeh AA, Eisen MB, Davis RE*, et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; 403(6769):503-11.

16. Lenz G, Wright GW, Emre NC*, et al.* Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci U S A* 2008; 105(36):13520-5.

17. 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(17):5494-502.

18. Gutiérrez-García G, Cardesa-Salzmann T, Climent F*, et al.* Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Blood* 2011; 117(18):4836-43.

19. Hans CP, Weisenburger DD, Greiner TC*, 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.

20. Meyer PN, Fu K, Greiner TC*, et al.* Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. *J Clin Oncol* 2011; 29(2):200-7.

21. Montes-Moreno S, Martinez N, Sanchez-Espiridion B*, et al.* miRNA expression in diffuse large B-cell lymphoma treated with chemoimmunotherapy. *Blood* 2011; 118(4):1034-40.

22. de Jong D, Rosenwald A, Chhanabhai M*, et al.* Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. *J Clin Oncol* 2007; 25(7):805-12.

23. Salles G, de Jong D, Xie W*, et al.* Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood* 2011; 117(26):7070-8.

24. Delecluse HJ, Anagnostopoulos I, Dallenbach F*, et al.* Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood* 1997; 89(4):1413-20.

25. Delsol G, Lamant L, Mariame B*, et al.* A new subtype of large B-cell lymphoma expressing the ALK kinase and lacking the 2; 5 translocation. *Blood* 1997; 89(5):1483-90.

26. Laurent C, Do C, Gascoyne RD*, et al.* Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma: a rare clinicopathologic entity with poor prognosis. *J Clin Oncol* 2009; 27(25):4211-6.

27. Cesarman E, Nador RG, Aozasa K*, et al.* Kaposi's sarcoma-associated herpesvirus in non-AIDS related lymphomas occurring in body cavities. *Am J Pathol* 1996; 149(1):53-7.

28. Du MQ, Liu H, Diss TC*, et al.* Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. *Blood* 2001; 97(7):2130-6.

29. Oksenhendler E, Boulanger E, Galicier L*, et al.* High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002; 99(7):2331-6.

30. Ott G, Ziepert M, Klapper W*, et al.* Immunoblastic morphology but not the immunohistochemical GCB/nonGCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL. *Blood* 2010; 116(23):4916-25.

31. Montes-Moreno S, Montalbán C, Piris MA. Large B-cell lymphomas with plasmablastic differentiation: a biological and therapeutic challenge. *Leuk Lymphoma* 2011.

32. Montes-Moreno S, Gonzalez-Medina AR, Rodriguez-Pinilla SM*, et al.* Aggressive large B-cell lymphoma with plasma cell differentiation: immunohistochemical characterization of plasmablastic lymphoma and diffuse large B-cell lymphoma with

partial plasmablastic phenotype. *Haematologica-the Hematology Journal* 2010; 95(8):1342-9.

33. Gascoyne RD, Lamant L, Martin-Subero JI*, et al.* ALK-positive diffuse large B-cell lymphoma is associated with Clathrin-ALK rearrangements: report of 6 cases. *Blood* 2003; 102(7):2568-73.

34. Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8-9 September 2008. *Ann Oncol* 2009; 20(9):1472-82.

35. Nakamura S JE, Swerdlow SH. *EBV positive diffuse large B-cell lymphoma of the elderly.*: Lyon, 2008.

36. Oyama T, Ichimura K, Suzuki R*, et al.* Senile EBV+ B-cell lymphoproliferative disorders: a clinicopathologic study of 22 patients. *Am J Surg Pathol* 2003; 27(1):16-26.

37. Dojcinov SD, Venkataraman G, Pittaluga S*, et al.* Age-related EBV-associated lymphoproliferative disorders in the Western population: a spectrum of reactive lymphoid hyperplasia and lymphoma. *Blood* 2011; 117(18):4726-35.

38. Hofscheier A, Ponciano A, Bonzheim I*, et al.* Geographic variation in the prevalence of Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: a comparative analysis of a Mexican and a German population. *Mod Pathol* 2011; 24(8):1046-54.

39. Santiago Montes-Moreno LO, Julio Alexander Diaz-Perez, Ana Batlle Lopez, Sonia Gonzalez de Villambrosía , Francisco Mazorra, Maria E. Castillo, Mar Lopez , Raquel Pajares, Juan F. García, Manuela Mollejo, Francisca I. Camacho, Carmen Ruiz-Marcellán, Magdalena Adrados, Nazario Ortiz, Renato Franco, Carlos Ortiz-Hidalgo, Ana Suarez-Gauthier, Ken H Young , Miguel A. Piris. EBV-positive Diffuse Large B Cell Lymphoma of the elderly is an agressive post-germinal center B cell neoplasm characterized by prominent Nuclear Factor-kB activation., Modern Pathology2012.

40. Cong P, Raffeld M, Teruya-Feldstein J*, et al.* In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. *Blood* 2002; 99(9):3376-82.

41. Adam P, Katzenberger T, Eifert M*, et al.* Presence of preserved reactive germinal centers in follicular lymphoma is a strong histopathologic indicator of limited disease stage. *Am J Surg Pathol* 2005; 29(12):1661-4.

42. Jegalian AG, Eberle FC, Pack SD*, et al.* Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. *Blood* 2011; 118(11):2976-84.

43. Montes-Moreno S, Castro Y, Rodriguez-Pinilla SM*, et al.* Intrafollicular neoplasia/in situ follicular lymphoma: review of a series of 13 cases. *Histopathology* 2010; 56(5):658-62.

44. Bonzheim I, Salaverria I, Haake A*, et al.* A unique case of follicular lymphoma provides insights to the clonal evolution from follicular lymphoma in situ to manifest follicular lymphoma. *Blood* 2011; 118(12):3442-4.

45. Campo E, Swerdlow SH, Harris NL*, et al.* The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; 117(19):5019-32.

46. Roulland S, Navarro JM, Grenot P*, et al.* Follicular lymphoma-like B cells in healthy individuals: a novel intermediate step in early lymphomagenesis. *J Exp Med* 2006; 203(11):2425-31.

47. Carvajal-Cuenca A, Sua LF, Silva NM*, et al.* In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. *Haematologica* 2011.

48. Espinet B, Solé F, Pedro C*, et al.* Clonal proliferation of cyclin D1-positive mantle lymphocytes in an asymptomatic patient: an early-stage event in the development or an indolent form of a mantle cell lymphoma? *Hum Pathol* 2005; 36(11):1232-7.

49. Nodit L, Bahler DW, Jacobs SA, Locker J, Swerdlow SH. Indolent mantle cell lymphoma with nodal involvement and mutated immunoglobulin heavy chain genes. *Hum Pathol* 2003; 34(10):1030-4.

50. Lecluse Y, Lebailly P, Roulland S*, et al.* t(11;14)-positive clones can persist over a long period of time in the peripheral blood of healthy individuals. *Leukemia* 2009; 23(6):1190-3.

51. Landgren O, Albitar M, Ma W*, et al.* B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med* 2009; 360(7):659-67.

52. Nieto WG, Almeida J, Romero A*, et al.* Increased frequency (12%) of circulating chronic lymphocytic leukemia-like B-cell clones in healthy subjects using a highly sensitive multicolor flow cytometry approach. *Blood* 2009; 114(1):33-7.

53. Shanafelt TD, Ghia P, Lanasa MC, Landgren O, Rawstron AC. Monoclonal B-cell lymphocytosis (MBL): biology, natural history and clinical management. *Leukemia* 2010; 24(3):512-20.

54. Gibson SE, Swerdlow SH, Ferry JA*, et al.* Reassessment of small lymphocytic lymphoma in the era of monoclonal B-cell lymphocytosis. *Haematologica* 2011; 96(8):1144-52.