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Published in final edited form as:

Title: B-cell lymphomas with discordance between pathological features and clinical behavior.

Authors: de Leval L, Copie-Bergman C, Rosenwald A, Rimsza L, Pittaluga S, Bisig B, Dirnhofer S, Facchetti F, Pileri S, Fend F, Wotherspoon A

Journal: Virchows Archiv : an international journal of pathology

Year: 2017 Jun 1

DOI: 10.1007/s00428-017-2152-9

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Virchows Archiv

B-CELL LYMPHOMAS WITH DISCORDANCE BETWEEN PATHOLOGICAL FEATURES AND CLINICAL BEHAVIOUR

--Manuscript Draft--

Manuscript Number:	VIAR-D-17-00143R1
Full Title:	B-CELL LYMPHOMAS WITH DISCORDANCE BETWEEN PATHOLOGICAL FEATURES AND CLINICAL BEHAVIOUR
Article Type:	Original Article
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Funding Information:	
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B-CELL LYMPHOMAS WITH DISCORDANCE BETWEEN PATHOLOGICAL FEATURES AND CLINICAL BEHAVIOUR

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Abstract

B-cell lymphomas encompass a large number of disease entities clinically ranging from indolent to aggressive. The defining pathological features usually predict clinical course, with small and large B-cell lymphomas correlating to low-grade versus high-grade features, but discordant situations may be encountered. Two sessions of the workshop of the XVIII meeting of the European Association for Haematopathology (EAHP) held in Basel in 2016 addressed this topic. One session illustrated various facets of "aggressiveness" in indolent lymphomas, either peculiar clinical manifestations, cytological variants or unusual genetic features, as well as several examples of progression or transformation to a more aggressive disease. Another session exemplified large B-cell lymphomas with unexpected indolent behavior including cases arising in well-defined body compartments or in sanctuary sites. This paper describes the features of the cases presented in both groups, highlights the most salient points of discussion raised by the submitters and the panel, and summarizes current knowledge and recommendations relevant to diagnostic pathology practice.

Introduction

Indolent lymphoma is defined as a lymphoma which tends to grow and spread slowly and has few symptoms usually not requiring immediate chemotherapeutic intervention ("low-grade"). Conversely, aggressive lymphomas are associated with a rapid growth and progressive clinical course ("high-grade"). These definitions, based on clinical presentation, clinical course and biological features, correspond to two broad categories of diseases and pathological entities [52].

Indolent lymphoma equates to small B-cell lymphoma entities, the most frequent and prototype being follicular lymphoma, followed by small lymphocytic lymphoma/chronic lymphocytic leukemia, lymphoplasmacytic lymphoma, marginal zone lymphoma (of extranodal, nodal and splenic types) and hairy cell leukemia [23]. Mantle cell lymphoma, although composed usually of small B cells, is typically characterized by an aggressive behavior. Despite slow disease evolution and treatment responsiveness, indolent lymphomas essentially represent incurable chronic diseases. They may pose clinical issues due to the tumor mass, or a more rapidly evolving disease with treatment resistance in some instances, and there is a cumulative risk of transformation to a high-grade lymphoma [52, 19].

Diffuse large B-cell lymphomas represent the prototype of aggressive B-cell lymphomas, which in principle require immediate treatment often with poly-chemotherapy associated with an immunological agent, resulting in long-term remission/cure in more than 50% of the patients. However, there is a group of lymphomas that have high-grade morphological features and indolent clinical behaviour, which typically arise in well-defined body compartments or in sanctuary sites.

This paper summarizes two sessions of the workshop of the XVIII meeting of the European Association for Haematopathology (EAHP) held in Basel in 2016. These sessions of the workshop were dedicated to B-cell lymphomas with discordance between pathological features and clinical behaviour. One session comprised 47 cases illustrating various facets of "aggressiveness" in indolent lymphomas, either peculiar clinical manifestations, cytologic variants or unusual genetic features, as well as several examples of progression or transformation to a more aggressive disease. The other session comprised 13 cases exemplifying large B-cell lymphomas with unexpected

indolent behaviour.

INDOLENT LYMPHOMAS WITH AGGRESSIVE FEATURES

Follicular lymphomas

Follicular lymphoma (FL) is one of the most common non-Hodgkin lymphomas (NHL) in Western countries accounting for 20-30% of adult lymphomas and 70% of indolent NHLs [52]. FL typically exhibits a follicular growth pattern and is composed of centrocytes admixed with a variable proportion of centroblasts. The cells have a CD20+ CD5- CD10+, BCL6+, BCL2+ immunophenotype and 80-90% carry the t(14;18)(q32;q21) *IGH-BCL2* translocation. Progression of FL usually refers to transition from grade ½ to 3A or evolution to a more diffuse growth pattern, while transformation is defined by a diffuse high-grade B-cell lymphoma. In addition, FL may display a variety of features suggestive of more aggressive behavior.

Follicular lymphoma with double/triple hit *MYC/BCL2/BCL6*

Four cases of *de novo* FL with double-hit (DH) *BCL2/MYC* (#321, P. Mroz) or triple-hit (TH) *BCL2/BCL6/MYC* (#102, G. Caponetti; #386, D. Weisenburger; #171, P. Farinha) rearrangements were reviewed by the panel. In contrast to these aggressive cytogenetic features, all of them were *de novo* non-transformed FL, grade 1/2 (n=3) or grade 3A (n=1), with classical CD20+, CD3-, CD10+, BCL6+, BCL2+ immunophenotype. MYC protein expression was less than 10% in 2 cases and expressed in 80% of the tumor cells in the other 2 cases, and the proliferative index (PI) evaluated by Ki67 immunostaining ranged from 10% to 80%. The *MYC* partner gene could be investigated in 3 of 4 cases and was of *non-IG* subtype (including the *CD96* gene) in the 2 cases with <10% MYC protein positive tumor cells, and *IGH* in one case with high MYC expression. One patient had localized disease but three patients presented with asymptomatic stage IV disease, including one patient with exclusively skeletal disease and multiple bone lesions who remained untreated for 1 year before being lost to follow-up (#102). Interestingly, one patient with TH FL relapsed at 9 years with a FL 1/2 carrying an isolated *BCL2* break and experienced complete remission without therapy (#171). None of the three patients with available follow-up had an aggressive clinical course.

MYC translocation in *de novo* non-transformed FL 1-2/3A is a rare event. Six cases of FL with *MYC* rearrangement and germline *BCL2* gene have been described with a follicular and diffuse architecture, grade 1 to 3 morphology and an indolent behaviour [34]. Less than 20 well documented cases of FL 1/2 with double-Hit *MYC/BCL2* have been published including a recent series of 7 patients (median age 47 years with a male predominance) with stage IV nodal and extranodal disease [37]. The DH FL were grade 1-2 to 3A with a follicular growth pattern, without any blastoid morphological features, classical immunophenotype, MYC protein expression <30% and Ki67 ranging from 5-50%. Three patients treated with standard regimen for FL had a poor outcome and 4 patients treated with a more intensive regimen for DH lymphoma achieved complete remission. In total, DH/TH *de novo* FL patients' prognosis remains unpredictable with either unexpectedly good outcome as in the cases submitted to the workshop, or more aggressive behavior as recently reported [37].

FL with high proliferative index

Two cases of FL with high Ki67 PI were submitted: one extranodal BCL2-negative (with clones 124 and E17 antibodies) FL 1/2 without detectable *BCL2* and *BCL6* breaks with bilateral breast involvement in a 82 year-old man (#256, W. Xue) and one disseminated FL 1/2 with a classical immunophenotype, t(14;18) positive in a 66 year-old man (#318, N. Panesar). The latter case displayed follicles with a starry-sky appearance, a proliferative index of 100% and was extensively documented by array-CGH analysis showing gains of 7q31, losses at 1p36 and 9p24 (*CDKN2A, CDKN2B*). The patient responded well to 6 cycles of R-bendamustine followed by rituximab maintenance therapy.

Ki67 index correlates in general with the FL grade but a high Ki67 level (30 to 40% or more) is observed in up to 20 percent of FL 1/2. As recommended in the report of the Istanbul EAHP meeting, the WHO grading should be retained for such cases with an additional comment that FL 1/2 with high PI might pursue a more aggressive course [59]. Delineation of these forms from FL with blastoid features is also important. Currently the prognostic significance remains controversial. Blastoid features refer to cytological features reminiscent of precursor cells, i.e. medium-sized cells with finely distributed chromatin and occasional presence of small nucleoli, resembling lymphoblasts or small centroblasts. As emphasized in the past [61], there is poor

reproducibility in recognition of this variant, and accordingly several cases submitted to the workshop where either not recognized as blastoid by the submitter and designated as such by the panel, or *vice-versa*. When blastoid features are encountered, the first step is to rule out transformation to a high-grade lymphoma, or lymphoblastic lymphoma (by performing TdT staining); in the context of follicular lymphoma, the term "follicular lymphoma not gradable with blastoid features" is recommended [61].

FL with *BCL2* or *NOTCH* gene mutations

FL may be associated with different mutational profiles with variable prognostic significance. Three cases were submitted with acquired *BCL2* or *NOTCH* mutations, or with inherited *TP53* mutation in the context of Li Fraumeni syndrome for one case. One case of *BCL2*-mutated FL grade 1/2 (#112, RL. King) occurred in a 42-year-old male, who presented with pancytopenia, extensive lymphadenopathy and died after 6 years following 6 different lines of therapy including autologous cell transplant. *BCL2* coding sequence mutations are reported to occur in 12% of FL 1/2 at diagnosis using Sanger sequencing. Mutations in the region of *BCL2* coding for the epitope recognized by the common anti-BCL2 antibody may cause false negative immunohistochemistry results, and alternative antibodies recognizing other epitopes may be necessary to demonstrate BCL2 expression in these cases [1, 51]. FL with *BCL2* mutations have been associated with increased risk of transformation and shortened survival in a retrospective series of *de novo* FL treated in the pre-rituximab era [11]. However, more sensitive deep DNA sequencing methods have shown up to 76% *BCL2* mutation rates in FL [42] and further studies are warranted to confirm the prognostic value of *BCL2* mutations in FL patients treated with rituximab-containing chemotherapy.

One case highlighted the peculiar features of *NOTCH*-mutated FL (#266, F. Sen). In this 43 year-old woman a cervical lymph node biopsy was first performed showing a *NOTCH1*-mutated B-cell lymphoma with a marginal zone pattern and increased large cells. Splenectomy performed a few months later displayed a CD10-, BCL2-, t(14;18) negative FL 1/2 with a high proliferative index (Figure 1). Although the relationship between the 2 diseases was difficult to assess on morphological grounds, additional studies performed by the panel showed that they were clonally related. *NOTCH* mutations occur in about 6% of FLs, are associated with a female predominance, lower

frequency of t(14;18), higher incidence of spleen involvement, and a significant association with DLBCL [31]. *NOTCH* mutations do not seem to have a prognostic impact in FL but additional studies on larger series are needed.

Transformed FL

Eleven cases of transformed FL (tFL) were submitted to the workshop. FL transformation into more aggressive lymphoma is observed in 2% to 3% of patients per year [33, 61]. FL transforms into different histologic subtypes, including DLBCL, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (formerly BCLu) or with blastoid morphology (TdT-negative) and lymphoblastic type (TdT-positive) lymphoma. According to the WHO 2016 update, the former BCLu cases are now distributed into 2 new categories: high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* translocations (for those carrying double-hit=DH or triple Hit=TH) and HGBL-not otherwise specified (NOS) for the others [54]. The morphologic subtype (DLBCL vs BCLu vs blastoid vs lymphoblastic) and the statement "transformed from FL" should be added in the pathology report (example: HGBL, with *BCL2* and *MYC* rearrangement, DLBCL morphology, transformed from FL"). It is recommended to demonstrate the clonal relationship between the 2 components. Importantly, HGBL-DH should be restricted to mature aggressive lymphomas and therefore excludes FL and lymphoblastic lymphomas with DH/TH. The 11 tFL submitted to the workshop included 2 DLBCL associated with FL and 9 HGBL-DH/TH with DLBCL (n= 7), BCLu (n=1) or blastoid morphology (n=1) (#263, R. Felgar)(Figure 2). In most HGBL, FL and HGBL components were diagnosed simultaneously at different sites, with FL in nodal or extranodal (lung, spleen, salivary gland) locations and HGBL in the bone marrow (BM) being the most frequent scenario, highlighting the importance of staging bone marrow biopsy. Only two cases had HGBL nodal involvement with concurrent FL in the bone marrow. One case with FL 1/2 in the spleen had BM and leukemic dissemination of the HGBL (#280, SS. Chuang).

Interestingly, in 2 cases the tFL was EBV-associated. Acquisition of EBV during transformation is overall a rare event and might be confused with the probably more frequent reactivation of intra- and peritumoral EBV in non-neoplastic cells. Case 105 (M. Tinguely) was a 50 year-old male who presented initially with nodal EBV+ DLBCL NOS

with *BCL2/BCL6* rearrangements and who achieved complete remission following R-CHOP therapy. He relapsed 2 years later with EBV-negative clonally related FL 1/2 carrying *BCL2/BCL6* breaks. Case 355 (D. De Jong) was a 74 year-old male with nodal EBV+ HGBL-DH *MYC/BCL2* with DLBCL morphology and FL 1/2 in the BM. Latency III EBV infection was demonstrated in tumor cells (LMP+, EBNA2+, EBERs+) questioning whether this case should be included in the HGBL or EBV+ DLBCL NOS category, and the potential role of EBV in HGBL transformation in these two cases.

Regarding the molecular subtypes of tFL, 9 were germinal center-like (GC) and the 2 EBV-associated tFL were non-germinal center-like (NGC) according to Hans algorithm [26]. This is consistent with the literature where tFL have been reported as germinal center (GC), activated B-cell type (ABC) or unclassified in 80%, 16% and 4% respectively using transcriptomic analysis [33]. Four out of 6 patients with clinical follow-up died, one had progressive disease and one achieved complete remission (case 295, 7 months follow-up).

Lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma (LPL) is a neoplasm of small lymphocytes, plasmacytoid, lymphocytes and plasma cells, usually involving the bone marrow and sometimes lymph nodes and spleen, which does not fulfill the criteria for other small B-cell lymphomas that may have plasmacytic differentiation (Figure 3A and 3C) [53]. The majority of LPL patients have Waldenström's macroglobulinemia, (WM) (defined as bone marrow involvement by LPL and a IgM serum paraprotein of any concentration) but this feature is not mandatory for LPL diagnosis [53]. More than 90% of LPL have MYD88 L265P mutation, but this abnormality is not specific as it is also encountered in other small B-cell lymphomas and a subset of DLBCLs [55]. About 30% of the patients harbor somatic mutations in *CXCR4* (most commonly the nonsense truncating S338X, or frameshift mutations in the C-terminal domain) in addition to the activating MYD88 L265P mutation, and this genotype tends to correlate with higher disease activity [50]. The uncommon cases with wild-type *MYD88* and those with *CXCR4* mutations have reduced responsiveness to Bruton's tyrosine kinase inhibitor ibrutinib [57, 58, 50].

The Bing-Neel syndrome designates a very rare manifestation of WM with neurological symptoms, due to infiltration of the central nervous system by

lymphoplasmocytoid cells, or due to humoral factors in the absence of cellular infiltrate of the brain or cerebrospinal fluid [38, 17]. Case #202 submitted by L. Venkatraman illustrated an example of this complication in a patient who presented with depression, headache and visual symptoms four years after a diagnosis LPL/WM. Imaging abnormalities were detected by MRI but no abnormal cellular infiltrate was definitively demontrated. Bing-Neel syndrome by definition excludes cases of transformation to high-grade lymphoma, but this patient later developed transformation to DLBCL involving the lacrimal gland and the brain.

Transformation of LPL to DLBCL occurs rarely (cumulative incidence <5% at 15 years) and is associated with a bad outcome [9, 35]. Development of Hodgkin lymphoma has been reported rarely in LPL patients [46]. Five cases of transformed LPL were submitted to the workshop (#171, M. Buehler; #238, L. Venkatraman; #202, C. Dommann-Scherrer; #332, T.N. Aladily; #252, H. Van Krieken). The patients had a 5 to 15 years history of LPL and four had WM. Among 4 cases tested for mutations, all were positive for MYD88 L265P, 3 were wild-type for *CXCR4* and 1 had a *CXCR4* frameshift mutation. Transformation was observed in lymph nodes in three patients and in extranodal sites in two. Histology at transformation was DLBCL in 4 cases including a case of plasmablastic lymphoma (figure 3A-B), and there was an exceptional case of clonally related EBV-positive lymphoproliferation with Hodgkin-like features in one patient who had undergone stem cell transplantation for disseminated LPL (#252) (Figure 3C-F). *MYC* rearrangement was documented in 2 DLBCL cases at transformation. Three of the patients with transformation to DLBCL died of disease, sometimes after prolonged evolution, but one patient is alive with disease persistent in the form of low-grade LPL one year after transformation and chemotherapy.

LPL may include an increased proportion of large cells, and there are no precise guidelines as to the threshold to consider transformation to DLBCL. Two cases were submitted (#317, D. Gur and #364, E. Mason), that were considered by the panel to represent LPL enriched in large cells. Both patients had massive bone marrow involvement, comprising an admixture of small and larger blastic cells. The latter, however, did not form confluent sheets and based on this, it was felt that the diagnosis of DLBCL was not warranted. One of those patients had a long history of LPL with multiple lines of therapy, and *MYD88* mutated/*CXCR4* wild-type genotype together with an *ARID1* mutation (Figure 3G-H). A biopsy in a second patient was obtained three

months after initial diagnosis and after worsening of anemia, a peculiar feature in this case was the demonstration of an as yet unreported genotype (*MYD88* wild-type/*CXCR4* frameshift mutation).

B-cell leukemias

Small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL/SLL) is an indolent neoplasm of small mature CD5+ CD23+ B-cells, with a small proportion of prolymphocytes distributed within proliferation centres seen in tissue sections [53]. Clinical progression has been associated with histologically aggressive forms, characterized by expanded proliferation centers or increased proliferation fraction (Ki67>40%) [15, 20] or an increased proportion of prolymphocytes (>10%) in the peripheral blood [40].

Transformation of CLL into an aggressive disease may result from prolymphocytoid transformation (defined by more than 55% prolymphocytes in the peripheral blood) or Richter's syndrome [53]. The two cases of prolymphocytoid transformation of CLL [#59, D. Grier and #170, B. Rea and A. Bagg] occurred at 10 and 13 years after CLL diagnosis and exhibited both typical peripheral blood morphology. In case #170 (Figure 4A) the karyotype obtained at transformation contained a t(8;14)(q24;q32) translocation, but neither *MYC* nor *IGH* were involved in the rearrangement, which was retrospectively found to be already present at CLL diagnosis. Interestingly a number of candidate oncogenes map to these loci (*ZHXQ* @ 8q24 and *TCL1* @ 14q32) and are possibly deregulated by the rearrangement.

Richter's syndrome (RS) is a term used to designate a clinical situation characterized by the sudden transformation into an aggressive disease in a patient with CLL/SLL, which occurs in 5- 10% of the cases [8, 3, 28]. Histologically, most cases are represented by DLBCLs but there is also a Hodgkin variant of RS accounting for a minority of the cases [41]. Although RS and "Richter transformation" seem to be used interchangeably in the literature, and most RS represent clonal evolution of the preexisting SLL/CLL, there is a subset of the cases that are clonally unrelated to the CLL and represent secondary malignancies. The latter includes a small proportion of DLBCLs and the majority of Hodgkin-type cases [12, 36]. Interestingly the two RS subsets

defined by clonal relationship are associated to distinct molecular features with a higher proportion of *TP53* alterations found in clonally related cases. There are different prognoses with clonally unrelated RS being associated to a significantly longer survival compared to clonally related RS who do very poorly [47]. Given the clinical impact of clonal relationship of the RS to the CLL, the panel recommended investigation of this feature in every case when possible and to restrict the use of the term "transformation" to cases that represent clonally-related lesions only. The definitive answer ultimately relies on molecular tests to compare the sequence of *VDJ* gene rearrangements or the genomic profiles of both lymphoproliferations.

One of the cases of RS (#273, M. Sharifian) was a classical example of a transformation to a DLBCL clonally related to the preexisting CLL, and associated to acquisition of *MYC* rearrangement, that occurred only two years after CLL diagnosis. The RS presented by D. Weisenburger (#384) occurred in a patient with SLL and no significant lymphocytosis, and consisted of EBV-negative *MYC*-rearranged plasmablastic lymphoma clonally unrelated to the preexisting SLL. There was a complex case of a composite lymphoma presented by A. Perry (#348) (Figure 4B-D): the initial lymph node in that patient comprised FL associated with an interfollicular involvement by SLL, plus foci of cyclinD1-positive *in situ* mantle cell neoplasia, harboring a *CCND1* rearrangement confirmed by FISH. Interestingly, although both the FL and SLL had distinct immunophenotypes, a PCR analysis for *IGH* gene rearrangement demonstrated only a single band, and both components harbored a *BCL2-IGH* fusion. The patient's disease later evolved towards a lymphoma with the features of classical Hodgkin lymphoma, EBV-negative, and the panel was able to demonstrate the presence of *BCL2-IGH* fusion in the Reed-Sternberg cells. That represents an exceptional example of clonally related Hodgkin lymphoma complicating a composite lymphoma including t(14;18)-positive SLL.

B-cell prolymphocytic leukemia (B-PLL) is a neoplasm of B prolymphocytes affecting the peripheral blood, bone marrow and spleen, with prolymphocytes exceeding 55% of lymphoid cells in the peripheral blood [53]. Cases of CLL with increased prolymphocytes or prolymphocytoid transformation, as well as lymphoproliferations associated to a t(11;14) translocation fusing *IGH* and *CCND1* are by definition excluded [49]. Numerical or structural abnormalities of the *MYC* gene have been reported in B-

PLL [18], and were indeed present in the 3 cases submitted to the workshop. One case (#305, E. Hsi) (Figure 4E-G) with a complex karyotype including a t(8;14)(q24.1;q32) was characterized by a relatively low absolute lymphocytosis and a long indolent clinical course, prior to transformation to a clonally related plasmablastic lymphoma. Case (#302, X. Wu) with an extra *MYC* copy showed a typical prolymphocytic morphology in the blood and bone marrow (Figure 4H), had spleen involvement and a dismal prognosis.

An exceptional case of **hairy cell leukemia** presented by M. Piris (#169) showed massive splenic involvement by large blastic cells, while scattered smaller cells with a morphology of hairy cells were observed in the peripheral blood [30]. A *BRAF* mutation was demonstrated together with triple-hit involving *BCL2, BCL6* and *MYC* rearrangements. This situation generated discussions regarding the most appropriate classification of this case, as a high-grade B-cell lymphoma with triple hit, *versus* blastoid hairy cell leukemia. The latter designation was favored given that the peculiar clinical and pathological features of hairy cell leukemia were clearly present; that patient expired shortly after diagnosis.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is usually characterized by an aggressive behavior; however, subsets of MCL with an indolent behavior recognized over the past years, namely *in situ* mantle cell neoplasia and non-nodal, leukemic MCL are now individualized in the revised WHO classification [29, 48, 54]. Leukemic non-nodal MCL is usually positive for cyclin D1, carries the t(11;14) translocation, but tends to be negative for SOX11 [29, 54]. Despite a usually indolent clinical course, these cases may transform and one example was illustrated by case #133 (L. Soma and S. Chen) (Figure 5). The patient presented with a leukemic picture comprising two components, one of small CD5-positive cells, the other of larger blasts with cells carrying a *MYC* rearrangement. Two other cases were presented that illustrated situations where leukemic MCL could be confused with CLL. In one case there was absence of cyclin D1 expression despite *IGH-CCND1* rearrangement, in the other one due to absence of demonstrable *CCND1* rearrangement, that turned out to be cryptic on standard karyotype and not identified by FISH; in the latter case the clinical evolution was aggressive and the patient died of

disease at 8 months (#142, J.Cook).

Case #352 (E. Sabattini) exemplified a peculiar nodal MCL with mixed small cells and pleomorphic components, the latter showing a marginal zone pattern with IRTA-1 expression, SOX11 positivity and no detectable cyclin D1 expression despite the presence of a *CCND1* gene rearrangement evidenced by FISH. Similar cases of cyclin D1-protein-negative, t(11;14)-positive MCL have been previously reported and so far that phenomenon remains unexplained [48].

AGGRESSIVE LYMPHOMAS WITH INDOLENT CLINICAL BEHAVIOUR

Large B-cell lymphoma associated with thrombus, myxoma, or prosthesis in the heart

Primary cardiac lymphoma (PCL) is a rare disorder accounting for 1% of cardiac tumours and only 0.5% of extranodal lymphomas [22]. There have been reports of lymphomas that arise within the cardiac chambers with a particularly indolent course [25, 4]. Similar cases have been reported in association with cardiac prostheses, vascular grafts and around joint prostheses [10, 16]. In the heart the right side is involved more frequently than the left [25] and the lymphomas are often associated with atrial myxoma or prosthetic valves[4, 16]. PCL involving native heart valves is very uncommon [4, 7].

Two cases in the workshop illustrated the unique features of PCL (#117, A. Joshi; #337, A. Ruano). One case arose within a cardiac thrombus (#337) (figure 6), while the other was associated with thrombus attached to a bioprosthetic mitral valve [18]. The clinical presentation in both cases was rather non-specific including shortness of breath and pulmonary edema. This presentation is quite typical of PCL where the presentation is characteristically associated with effusions, constitutional symptoms and/or shortness of breath.

Morphologically, the cells in PCL are reported to be large and embedded in fibrin or thrombus without invasion of the myocardium. The cells have a typical B-cell immunophenotype and are generally non-germinal centre type. They are usually positive for EBV with a type III latency pattern [4, 7]. Both submitted cases showed clonal *IGH* gene rearrangement.

These two cases illustrate the indolent clinical course with one patient alive and disease free without any further treatment. The cases in the literature also show a favourable outcome and recognition of these PCLs is important to avoid potential overtreatment.

The pathogenesis of these lymphomas and the explanation for their unusually indolent behaviour remains unclear. Most cases arise in immunocompetent patients but it has been suggested that there may be localised reduction of immune surveillance confined to the location in which the lymphoma develops [4, 43]. This may be due to increased local concentrations of IL-6 as a result of local inflammatory response, increased concentration of IL-10 locally or by the sequestration of the neoplastic cells within clot that is not well penetrated by normal immune regulatory cells [4]. PCLs are more often encountered in older aged patients and age-related immune senescence should also be considered as a potential contributory factor [4]. These are very rare lymphomas but from the cases presented in the literature it can be postulated that complete resection of the thrombus and/or prosthesis may be curative avoiding the requirement for more aggressive poly-chemotherapy.

Effusion lymphoma associated with fluid overload

Primary effusion lymphoma (PEL) is a rare B-cell lymphoma that is confined to body cavities associated with pleural, pericardial serous effusions or with peritoneal ascites. Typically PEL is a human herpes virus 8 (HHV8)-related lymphoma encountered in the context of human immunodeficiency virus (HIV) infection that has a very poor outlook with median survival of 3-4 months. It is characterized by a proliferation of large cells morphologically intermediate between immunoblastic and anaplastic large cells. The cells tend to lack pan-B-cell antigens such as CD19, CD20 and CD79a while retaining expression of CD45 with positive staining for plasma cell and activation markers (CD38, CD138 and CD30). They show positive nuclear staining for HHV8-associated latent protein LANA and are negative for EBV.

Cavity-based B-cell lymphomas unrelated to HHV8 infection (HHV8-unrelated PEL-like lymphomas) may occur in other clinical scenarios [27, 60]. These may be divided into effusion-based Burkitt lymphoma (with *MYC* rearrangement, EBV-positive or negative) and effusion-based large B-cell lymphomas characterized by large cell

morphology, absence of *MYC* rearrangement but possibility of *MYC* amplification and variable EBV status. In contrast to classical PEL, the cells retain expression of pan-B cell markers while markers of plasma cell differentiation and activation are usually negative. The patients are usually older and the outlook is significantly superior to classical PEL with a median survival up to 10 months, while a 35% 1-year survival has been reported.

HHV8-unrelated PEL-like lymphoma was illustrated by one case (#313, M.F. van den Hout). The patient was an elderly (85yrs) male with massive pericardial effusion but without significant previous medical history and tested negative for HIV. The pericardial effusion was drained and microscopic examination revealed a population of large cells, many with immunoblastic morphology. The cells stained for CD20 and CD79a while they were negative for CD138, CD30, HHV8 and EBER. Due to the advanced age of the patient and the lack of other symptoms or evidence of disseminated disease no further intervention was undertaken and the patient was alive and apparently disease free 3 months later.

This case highlighted many of the features that distinguish classical PEL from PEL-like lymphoma. PEL-like lymphoma typically presents at an older age and is usually associated with disorders that are associated with serous effusions such as heart failure or cirrhosis [5, 60]. The aetio-pathogenesis of the lymphoma is unclear but is unrelated to HIV or HHV8 [5, 60]. There has been a reported association with hepatitis C virus [27, 45] and a proportion may be related to EBV [60, 56]. Due to the rarity of these lymphomas the optimal therapy is unclear. Many patients may be unsuitable for aggressive therapy but where appropriate poly-chemotherapy may be used in combination with anti-CD20 immunotherapy [45, 60]. It has been suggested that many cases may be undiagnosed as the effusion may be dismissed as being related to heart-failure and there are cases, such as the one submitted to the workshop, that have received no active therapy and have regressed following fluid drainage with or without pleurodesis [45]. A useful diagnostic test may be fluid to serum LDH ratio which has been reported to be very high in these cases [45].

Large B-cell lymphoma confined to peripheral nerve

Neurolymphomatosis (NL) designates the presence of infiltration of nerve trunks, nerve roots, plexi and cranial nerves by lymphoma cells [24]. NL is rare and may occur as part

of disseminated lymphoma but less commonly the lymphomatous infiltrate is confined to a peripheral nerve (primary lymphoma of peripheral nerve, PLPN) [13] with a high proportion of the cases described in the literature involving the sciatic nerve [2]. Almost all of the cases of PLPN have been DLBCL [21]. The age of presentation is usually 34-72 years (mean 57.3 years) with a higher incidence in men [21]. Deletion of the *CDKN2A/p16* gene has been described in some cases and may be a negative prognostic factor [39, 14]. A pre-existing history of auto-immune disease has been suggested as a predisposing factor [39, 14]. Possible explanations for location in peripheral nerve may include the presence of B cells within the peripheral nerve [44] or the expression of specific adhesion molecules [6].

A single case of PLPN was submitted to the workshop (#350, S. Dojcinov). The patient presented with pain in the left upper forearm and hand consistent with carpal tunnel syndrome. Decompression was performed but the symptoms progressed with flail arm and muscle wasting. Subsequent imaging studies revealed thickening of the brachial plexus with increased PET activity confined to the brachial plexus and median nerve. A nerve biopsy revealed DLBCL with expression of CD20, BCL6, BCL2 and MUM1 while the cells were negative for CD10, CD5, CD23, CD43 and EBER.

The case illustrated many of the typical features seen in PLPN. Reaching the correct diagnosis is often difficult and usually requires nerve biopsy or large resection. In some cases the lesion may be mass-forming and misdiagnosed as schwannoma [32]. Most cases are treated as usual DLBCLs [24, 2, 14]. The case submitted to the workshop was treated with six cycles of R-CHOP chemotherapy with intra-thecal prophylaxis to complete response but relapsed 24 months later with contralateral brachial plexus involvement that was treated with intensified chemotherapy and autologous stem cell transplant resulting in remission that has extended so far for a further 12 months. This clinical behaviour is in contrast to many of the cases reported in the literature where the clinical outlook for NL is generally poor with median survival of around 10 months [24]. There are frequent relapses in the central nervous system. However there is possibly a better prognosis for primary compared to secondary NL [24].

Conclusions

Some cases of indolent lymphomas encompass a spectrum of morphological, immunophenotypical and genetic/molecular features that might suggest a potentially more aggressive behavior. All features must be interpreted in the light of the morphology and clinical context. In particular *MYC* rearrangement may be observed in *de novo* low-grade B-cell lymphomas, in the absence of histological transformation; such a finding should be mentioned in the diagnostic report but is not necessarily indicative of an increased risk of clinical progression.

Transformation of indolent to aggressive B-cell lymphomas comprises a cytological spectrum including large cell, blastoid, Burkitt-like, prolymphocytoid or even Hodgkin-like proliferations. In follicular lymphomas, DLBCL not otherwise specified and high-grade B-cell lymphoma double-hit represent the most common forms of transformation. The basis for considering histological transformation is the identification of sheets of large transformed cells. There remains a category of "intermediate" cases with an increased number of large cells not considered sufficient to warrant a diagnosis of transformation that are difficult to interpret. Although the high-grade transformation is usually clonally related to the preexisting small B-cell lymphoma, a subset of the cases represent clonally unrelated events, a distinction that is important to assess given the distinct clinical behavior and prognosis in clonally related versus unrelated cases, especially in the context of Richter's syndrome.

Among large B-cell lymphomas, those that develop as localized disease in association with thrombi, myxoma or prosthesis in the heart appear to run an indolent clinical course with the option for localized treatment (e.g. resection of thrombus and/or prosthesis); among lymphomatous proliferations associated with effusions, those with "PEL-like" features associated with fluid overload and unrelated to HHV8 infection may regress following fluid drainage and should be distinguished from the aggressive type of PEL lymphoma.

Acknowledgments

The authors thank the workshop participants for their case submissions and for use of their images in this review. Mrs. B. Pasche is acknowledged for her secretarial assistance in preparing the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

FIGURES LEGENDS

Figure 1

NOTCH mutated follicular lymphoma of the spleen (case #266, courtesy from Dr F. Sen).

H&E stains showing involvement of the white pulp of the spleen by a nodular lymphoid proliferation (A) composed of small atypical lymphoid cells (B). By immunohistochemistry, the lymphoid cells are positive for CD20 (C) negative for BCL2/clone 124 (D) and show a high Ki67 high proliferative index (E).

Figure 2

Transformed follicular lymphoma of the lymph node to high-grade B-cell lymphoma, triple-hit *BCL2 BCL6* and *MYC*, with blastoid morphology in the bone marrow (case #263, courtesy from Dr R. Felgar).

H&E stain showing involvement of an axillary lymph node by a grade ½ follicular lymphoma (A and B) with *BCL2* and BCL6 genes rearrangements (not shown), bone marrow aspirate showing replacement of normal elements by a blastoid population (C) and MYC immunohistochemistry on the bone marrow trephine biopsy showing diffuse and strong positivity (D).

Figure 3

Lymphoplasmacytic lymphoma.

(A-B) Case #171, courtesy of Dr. Bühler. Heavy bone marrow involvement by LPL composed of small lymphoid cells, lymphoplasmayctoid cells and plasma cells (A); and axillary lymph node biopsy with transformation to plasmablastic lymphoma, composed of large cells with immunoblastic morphology, abundant cytoplasm and a CD20- CD138+ immunophenotype showing the same light chain restriction as the LPL and a *MYC* rearrangement.

(C-F) Case #252 submitted by Dr. H. Van Krieken. The patient presented with nodal involvement by lymphoplasmacytic lymphoma containing cells with intranuclear inclusions (Dütcher bodies and arrows) (C); two years after autologous stem cell transplantation he developed a lymphoproliferation containing many atypical large cells

with Reed-Sternberg-like (HR-like) features and a CD30+ CD15+ EBV+ phenotype in a histiocytic background (D); immunostainings for Ig light chains demonstrated monotypic kappa restriction in the LPL (E) and the HRS-like cells (F) suggesting clonal relatedness between the two processes, which was further demonstrated by identical *IGH* gene rearrangement and the presence of MYD88 L285P variant in both biopsies.

(G-H) Case #317, submitted by Dr D. Gur. Bone marrow biopsy showing massive infiltrate by LPL comprising an increased proportion of large cells (G) with a Ki67 proliferation index averaging 50%.

Figure 4

Small lymphocytic lymphoma/Chronic lymphocytic leukemia (SLL/CLL) and B-cell prolymphocytic leukemia (B-PLL) (A). Prolymphoid transformation of CLL (case #170, courtesy of Drs B. Rea and A. Bagg): peripheral blood smears showing a majority of prolymphocytes characterized by prominent nucleoli.

(B-D) Hodgkin variant of Richter's syndrome (case #348, courtesy of Dr A. Perry). Lymph node involvement by a composite follicular lymphoma (upper left and lower right) and small lymphocytic lymphoma (interfollicular involvement) (B), later transformed to a lymphoproliferation with features of classical Hodgkin lymphoma (C). FISH analysis using a dual fusion probe *IgH*/*BCL2* demonstrated multiple fusion signals in the Reed-Sternberg cells, indicating clonal relationships to the preexisting small B-cell lymphoproliferation (D).

(E-G) B-cell prolymphocytic leukemia (case #305, courtesy of Dr E.D. Hsi). Bone marrow histology in a case of B-PLL showing an infiltrate of small to medium-sized lymphoid cells with prominent nucleoli (E) and strong MYC expression (F), peripheral blood smear showing lymphoid cells with prominent nucleoli (G).

(H) Bone marrow aspirate in a case of B-PLL with a massive splenomegaly, mild lymphocytosis and bone marrow involvement (case #302, courtesy of Dr X. Wu).

Figure 5

Leukemic mantle cell lymphoma transformed to blastoid variant with *MYC* and *CCND1* rearrangement (case #133, courtesy of Drs L. Soma and X. Chen).

Peripheral blood smear showing a dual population of small lymphoid cells and larger cells with blastoid morphology (upper and lower panels) (A).; bone marrow aspirate showing massive involvement by lymphoid cells with blastoid features (B); bone marrow histology showing diffuse replacement of the marrow spaces by monotonous population of medium-sized cells with blastoid features, displaying a starry-sky pattern (C); chromosome analysis showing a 46, XY, del (3) (q25, q26.2), t(8;14) (q24; q32), t(11; 14) (q13; q32) [5]/46, XY [15]; (E-H) Bone marrow immunohistochemistry: lymphoid cells are positive for CD10 (E), cyclin D1 (F), MYC (G) and p53 (H).

Figure 6

Cardiac thrombus associated large B-cell lymphoma (Case #337, courtesy of Dr. A. Ruano). Large lymphoid cells are embedded in a cardiac thrombus without invasion of the myocardium (A). Tumor cells show expression of CD20 (B), are positive in the EBER in situ hybridization (C) and show a high proliferative rate in the Ki67 stain (D).

References

1. Adam P, Baumann R, Schmidt J, Bettio S, Weisel K, Bonzheim I, Fend F, Quintanilla-Martinez L (2013) The BCL2 E17 and SP66 antibodies discriminate 2 immunophenotypically and genetically distinct subgroups of conventionally BCL2-"negative" grade 1/2 follicular lymphomas Hum Pathol 44:1817-1826. doi: 10.1016/j.humpath.2013.02.004
2. Advani P, Paulus A, Murray P, Jiang L, Goff R, Pooley R, Jain M, Garner H, Foran J (2015) A rare case of primary high-grade large B-cell lymphoma of the sciatic nerve Clin Lymphoma Myeloma Leuk 15:e117-120. doi: 10.1016/j.clml.2014.12.001
3. Agbay RL, Jain N, Loghavi S, Medeiros LJ, Khoury JD (2016) Histologic transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma Am J Hematol 91:1036-1043. doi: 10.1002/ajh.24473
4. Aguilar C, Beltran B, Quinones P, Carbajal T, Vilcapaza J, Yabar A, Segura P, Quintanilla-Martinez L, Miranda RN, Castillo JJ (2015) Large B-cell lymphoma arising in cardiac myxoma or intracardiac fibrinous mass: a localized lymphoma usually associated with Epstein-Barr virus? Cardiovasc Pathol 24:60-64. doi: 10.1016/j.carpath.2014.08.007
5. Alexanian S, Said J, Lones M, Pullarkat ST (2013) KSHV/HHV8-negative effusion-based lymphoma, a distinct entity associated with fluid overload states Am J Surg Pathol 37:241-249. doi: 10.1097/PAS.0b013e318267fabc
6. Baehring JM, Damek D, Martin EC, Betensky RA, Hochberg FH (2003) Neurolymphomatosis Neuro-oncology 5:104-115. doi: 10.1215/s1522-8517-02-00017-0
7. Boyer DF, McKelvie PA, de Leval L, Edlefsen KL, Ko YH, Aberman ZA, Kovach AE, Masih A, Nishino HT, Weiss LM, Meeker AK, Nardi V, Palisoc M, Shao L, Pittaluga S, Ferry JA, Harris NL, Sohani AR (2017) Fibrin-associated EBV-positive Large B-Cell Lymphoma: An Indolent Neoplasm With Features Distinct From Diffuse Large B-Cell Lymphoma Associated With Chronic Inflammation Am J Surg Pathol 41:299-312. doi: 10.1097/PAS.0000000000000775
8. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES (2011) The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications Blood 117:5019-5032. doi: 10.1182/blood-2011-01-293050
9. Castillo JJ, Gustine J, Meid K, Dubeau T, Hunter ZR, Treon SP (2016) Histological transformation to diffuse large B-cell lymphoma in patients with Waldenstrom macroglobulinemia Am J Hematol 91:1032-1035. doi: 10.1002/ajh.24477
10. Cheuk W, Chan AC, Chan JK, Lau GT, Chan VN, Yiu HH (2005) Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorax-associated lymphoma? Am J Surg Pathol 29:832-836
11. Correia C, Schneider PA, Dai H, Dogan A, Maurer MJ, Church AK, Novak AJ, Feldman AL, Wu X, Ding H, Meng XW, Cerhan JR, Slager SL, Macon WR, Habermann TM, Karp JE, Gore SD, Kay NE, Jelinek DF, Witzig TE, Nowakowski GS, Kaufmann SH (2015) BCL2 mutations are associated with increased risk of transformation and shortened survival in follicular lymphoma Blood 125:658-667. doi: 10.1182/blood-2014-04-571786
12. de Leval L, Vivario M, De Prijck B, Zhou Y, Boniver J, Harris NL, Isaacson P, Du MQ (2004) Distinct clonal origin in two cases of Hodgkin's lymphoma variant of Richter's syndrome associated With EBV infection Am J Surg Pathol 28:679-686
13. Del Grande A, Sabatelli M, Luigetti M, Conte A, Granata G, Rufini V, Del Ciello A, Gaudino S, Fernandez E, Hohaus S, Coli A, Lauriola L (2014) Primary multifocal lymphoma of peripheral nervous system: case report and review of the literature Muscle Nerve 50:1016-1022. doi: 10.1002/mus.24354
14. Descamps MJ, Barrett L, Groves M, Yung L, Birch R, Murray NM, Linch DC, Lunn MP, Reilly MM (2006) Primary sciatic nerve lymphoma: a case report and review of the literature Journal of neurology, neurosurgery, and psychiatry 77:1087-1089. doi: 10.1136/jnnp.2006.087577

15. Falchi L, Keating MJ, Marom EM, Truong MT, Schlette EJ, Sargent RL, Trinh L, Wang X, Smith SC, Jain N, Estrov Z, O'Brien S, Wierda WG, Lerner S, Ferrajoli A (2014) Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia Blood 123:2783-2790. doi: 10.1182/blood-2013-11-536169
16. Farah FJ, Chiles CD (2014) Recurrent primary cardiac lymphoma on aortic valve allograft: implications for therapy Tex Heart Inst J 41:543-546. doi: 10.14503/THIJ-13-3567
17. Fintelmann F, Forghani R, Schaefer PW, Hochberg EP, Hochberg FH (2009) Bing-Neel Syndrome revisited Clinical lymphoma & myeloma 9:104-106. doi: 10.3816/CLM.2009.n.028
18. Flatley E, Chen AI, Zhao X, Jaffe ES, Dunlap JB, Pittaluga S, Abdullah S, Olson SB, Spurgeon SE, Fan G (2014) Aberrations of MYC are a common event in B-cell prolymphocytic leukemia Am J Clin Pathol 142:347-354. doi: 10.1309/AJCPUBHM8U7ZFLOB
19. Gascoyne RD (2015) XIV. The pathology of transformation of indolent B cell lymphomas Hematol Oncol 33 Suppl 1:75-79. doi: 10.1002/hon.2222
20. Gine E, Martinez A, Villamor N, Lopez-Guillermo A, Camos M, Martinez D, Esteve J, Calvo X, Muntanola A, Abrisqueta P, Rozman M, Rozman C, Bosch F, Campo E, Montserrat E (2010) Expanded and highly active proliferation centers identify a histological subtype of chronic lymphocytic leukemia ("accelerated" chronic lymphocytic leukemia) with aggressive clinical behavior Haematologica 95:1526-1533. doi: 10.3324/haematol.2010.022277
21. Gonzalvo A, McKenzie C, Harris M, Biggs M (2010) Primary non-Hodgkin's lymphoma of the radial nerve: case report Neurosurgery 67:E872-873; discussion E873. doi: 10.1227/01.NEU.0000374852.65670.7D
22. Gowda RM, Khan IA (2003) Clinical perspectives of primary cardiac lymphoma Angiology 54:599-604. doi: 10.1177/000331970305400510
23. Gribben JG (2007) How I treat indolent lymphoma Blood 109:4617-4626. doi: 10.1182/blood-2006-10-041863
24. Grisariu S, Avni B, Batchelor TT, van den Bent MJ, Bokstein F, Schiff D, Kuittinen O, Chamberlain MC, Roth P, Nemets A, Shalom E, Ben-Yehuda D, Siegal T, International Primary CNSLCG (2010) Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report Blood 115:5005-5011. doi: 10.1182/blood-2009-12-258210
25. Gruver AM, Huba MA, Dogan A, Hsi ED (2012) Fibrin-associated large B-cell lymphoma: part of the spectrum of cardiac lymphomas Am J Surg Pathol 36:1527-1537. doi: 10.1097/PAS.0b013e31825d53b5
26. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Muller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO, Chan WC (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray Blood 103:275-282. doi: 10.1182/blood-2003-05-1545
27. Ichinohasama R, Miura I, Kobayashi N, Saitoh Y, DeCoteau JF, Saiki Y, Mori S, Kadin ME, Ooya K (1998) Herpes virus type 8-negative primary effusion lymphoma associated with PAX-5 gene rearrangement and hepatitis C virus: a case report and review of the literature Am J Surg Pathol 22:1528-1537
28. Jamroziak K, Tadmor T, Robak T, Polliack A (2015) Richter syndrome in chronic lymphocytic leukemia: updates on biology, clinical features and therapy Leuk Lymphoma 56:1949-1958. doi: 10.3109/10428194.2014.979411
29. Jares P, Colomer D, Campo E (2012) Molecular pathogenesis of mantle cell lymphoma J Clin Invest 122:3416-3423. doi: 10.1172/jci61272
30. Kanellis G, Garcia-Alonso L, Camacho FI, Garcia JF, Mollejo M, Montes-Moreno S, Garcia-Vela JA, Piris MA (2011) Hairy cell leukemia, blastic type: description of spleen morphology and immunophenotype of a distinctive case Leuk Lymphoma 52:1589-1592. doi: 10.3109/10428194.2011.575488
31. Karube K, Martinez D, Royo C, Navarro A, Pinyol M, Cazorla M, Castillo P, Valera A, Carrio A, Costa D, Colomer D, Rosenwald A, Ott G, Esteban D, Gine E, Lopez-Guillermo A, Campo E

(2014) Recurrent mutations of NOTCH genes in follicular lymphoma identify a distinctive subset of tumours J Pathol 234:423-430. doi: 10.1002/path.4428
32. Kim SK, Lee SH, Kim ES, Eoh W (2016) Diffuse Large B-Cell Lymphoma Mimicking Schwannoma of Lumbar Spine Korean Journal of Spine 13:71-73. doi: 10.14245/kjs.2016.13.2.71
33. Kridel R, Mottok A, Farinha P, Ben-Neriah S, Ennishi D, Zheng Y, Chavez EA, Shulha HP, Tan K, Chan FC, Boyle M, Meissner B, Telenius A, Sehn LH, Marra MA, Shah SP, Steidl C, Connors JM, Scott DW, Gascoyne RD (2015) Cell of origin of transformed follicular lymphoma Blood 126:2118-2127. doi: 10.1182/blood-2015-06-649905
34. Ladanyi M, Offit K, Parsa NZ, Condon MR, Chekka N, Murphy JP, Filippa DA, Jhanwar SC, Dalla-Favera R, Chaganti RS (1992) Follicular lymphoma with t(8;14)(q24;q32): a distinct clinical and molecular subset of t(8;14)-bearing lymphomas Blood 79:2124-2130
35. Lin P, Mansoor A, Bueso-Ramos C, Hao S, Lai R, Medeiros LJ (2003) Diffuse large B-cell lymphoma occurring in patients with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. Clinicopathologic features of 12 cases Am J Clin Pathol 120:246-253. doi: 10.1309/r01v-xg46-mfcd-vnhl
36. Mao Z, Quintanilla-Martinez L, Raffeld M, Richter M, Krugmann J, Burek C, Hartmann E, Rudiger T, Jaffe ES, Muller-Hermelink HK, Ott G, Fend F, Rosenwald A (2007) IgVH mutational status and clonality analysis of Richter's transformation: diffuse large B-cell lymphoma and Hodgkin lymphoma in association with B-cell chronic lymphocytic leukemia (B-CLL) represent 2 different pathways of disease evolution Am J Surg Pathol 31:1605-1614. doi: 10.1097/PAS.0b013e31804bdaf8
37. Miao Y, Hu S, Lu X, Li S, Wang W, Medeiros LJ, Lin P (2016) Double-hit follicular lymphoma with MYC and BCL2 translocations: a study of 7 cases with a review of literature Hum Pathol 58:72-77. doi: 10.1016/j.humpath.2016.07.025
38. Minnema MC, Kimby E, D'Sa S, Fornecker LM, Poulain S, Snijders TJ, Kastritis E, Kremer S, Fitsiori A, Simon L, Davi F, Lunn M, Castillo JJ, Patterson CJ, Le Garff-Tavernier M, Costopoulos M, Leblond V, Kersten MJ, Dimopoulos MA, Treon SP (2017) Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome Haematologica 102:43-51. doi: 10.3324/haematol.2016.147728
39. Misdraji J, Ino Y, Louis DN, Rosenberg AE, Chiocca EA, Harris NL (2000) Primary lymphoma of peripheral nerve: report of four cases Am J Surg Pathol 24:1257-1265
40. Oscier D, Else M, Matutes E, Morilla R, Strefford JC, Catovsky D (2016) The morphology of CLL revisited: the clinical significance of prolymphocytes and correlations with prognostic/molecular markers in the LRF CLL4 trial Br J Haematol 174:767-775. doi: 10.1111/bjh.14132
41. Parikh SA, Habermann TM, Chaffee KG, Call TG, Ding W, Leis JF, Macon WR, Schwager SM, Ristow KM, Porrata LF, Kay NE, Slager SL, Shanafelt TD (2015) Hodgkin transformation of chronic lymphocytic leukemia: Incidence, outcomes, and comparison to de novo Hodgkin lymphoma Am J Hematol 90:334-338. doi: 10.1002/ajh.23939
42. Pastore A, Jurinovic V, Kridel R, Hoster E, Staiger AM, Szczepanowski M, Pott C, Kopp N, Murakami M, Horn H, Leich E, Moccia AA, Mottok A, Sunkavalli A, Van Hummelen P, Ducar M, Ennishi D, Shulha HP, Hother C, Connors JM, Sehn LH, Dreyling M, Neuberg D, Moller P, Feller AC, Hansmann ML, Stein H, Rosenwald A, Ott G, Klapper W, Unterhalt M, Hiddemann W, Gascoyne RD, Weinstock DM, Weigert O (2015) Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry Lancet Oncol 16:1111-1122. doi: 10.1016/S1470-2045(15)00169-2
43. Petrich A, Cho SI, Billett H (2011) Primary cardiac lymphoma: an analysis of presentation, treatment, and outcome patterns Cancer 117:581-589. doi: 10.1002/cncr.25444
44. Quinones-Hinojosa A, Friedlander RM, Boyer PJ, Batchelor TT, Chiocca EA (2000) Solitary sciatic nerve lymphoma as an initial manifestation of diffuse neurolymphomatosis. Case

report and review of the literature Journal of neurosurgery 92:165-169. doi: 10.3171/jns.2000.92.1.0165
45. Raskin J, Slabbynck H, Beel K (2016) Human Herpes Virus 8 Unrelated Bilateral Primary Effusion Lymphoma in a Patient With Chronic Fluid Overload Arch Bronconeumol 52:492-493. doi: 10.1016/j.arbres.2015.12.012
46. Rosales CM, Lin P, Mansoor A, Bueso-Ramos C, Medeiros LJ (2001) Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia associated with Hodgkin disease. A report of two cases Am J Clin Pathol 116:34-40. doi: 10.1309/9dby-fbug-y10a-aaxt
47. Rossi D, Spina V, Deambrogi C, Rasi S, Laurenti L, Stamatopoulos K, Arcaini L, Lucioni M, Rocque GB, Xu-Monette ZY, Visco C, Chang J, Chigrinova E, Forconi F, Marasca R, Besson C, Papadaki T, Paulli M, Larocca LM, Pileri SA, Gattei V, Bertoni F, Foa R, Young KH, Gaidano G (2011) The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation Blood 117:3391-3401. doi: 10.1182/blood-2010-09-302174
48. Sander B, Quintanilla-Martinez L, Ott G, Xerri L, Kuzu I, Chan JK, Swerdlow SH, Campo E (2016) Mantle cell lymphoma--a spectrum from indolent to aggressive disease Virchows Arch 468:245-257. doi: 10.1007/s00428-015-1840-6
49. Schlette E, Bueso-Ramos C, Giles F, Glassman A, Hayes K, Medeiros LJ (2001) Mature B-cell leukemias with more than 55% prolymphocytes. A heterogeneous group that includes an unusual variant of mantle cell lymphoma Am J Clin Pathol 115:571-581. doi: 10.1309/PPK0-TJUK-1UAR-3194
50. Schmidt J, Federmann B, Schindler N, Steinhilber J, Bonzheim I, Fend F, Quintanilla-Martinez L (2015) MYD88 L265P and CXCR4 mutations in lymphoplasmacytic lymphoma identify cases with high disease activity Br J Haematol 169:795-803. doi: 10.1111/bjh.13361
51. Schraders M, de Jong D, Kluin P, Groenen P, van Krieken H (2005) Lack of Bcl-2 expression in follicular lymphoma may be caused by mutations in the BCL2 gene or by absence of the t(14;18) translocation J Pathol 205:329-335. doi: 10.1002/path.1689
52. Sehn LH (2016) Introduction to a review series: the paradox of indolent B-cell lymphoma Blood 127:2045-2046. doi: 10.1182/blood-2016-03-692442
53. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, Thiele J, Vardiman J (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues
54. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms Blood 127:2375-2390. doi: 10.1182/blood-2016-01-643569
55. Swerdlow SH, Kuzu I, Dogan A, Dirnhofer S, Chan JK, Sander B, Ott G, Xerri L, Quintanilla-Martinez L, Campo E (2016) The many faces of small B cell lymphomas with plasmacytic differentiation and the contribution of MYD88 testing Virchows Arch 468:259-275. doi: 10.1007/s00428-015-1858-9
56. Tanaka S, Katano H, Tsukamoto K, Jin M, Oikawa S, Nishihara H, Sawa H, Sawada K, Shimizu M, Sata T, Fujioka Y, Nagashima K (2001) HHV8-negative primary effusion lymphoma of the peritoneal cavity presenting with a distinct immunohistochemical phenotype Pathol Int 51:293-300
57. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR (2014) Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia Blood 123:2791-2796. doi: 10.1182/blood-2014-01-550905
58. Treon SP, Xu L, Hunter Z (2015) MYD88 Mutations and Response to Ibrutinib in Waldenstrom's Macroglobulinemia N Engl J Med 373:584-586. doi: 10.1056/NEJMc1506192
59. Wang SA, Wang L, Hochberg EP, Muzikansky A, Harris NL, Hasserjian RP (2005) Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features Am J Surg Pathol 29:1490-1496

60. Wu W, Youm W, Rezk SA, Zhao X (2013) Human herpesvirus 8-unrelated primary effusion lymphoma-like lymphoma: report of a rare case and review of 54 cases in the literature Am J Clin Pathol 140:258-273. doi: 10.1309/AJCPHZ3CHO4HUWET
61. Xerri L, Dirnhofer S, Quintanilla-Martinez L, Sander B, Chan JK, Campo E, Swerdlow SH, Ott G (2016) The heterogeneity of follicular lymphomas: from early development to transformation Virchows Arch 468:127-139. doi: 10.1007/s00428-015-1864-y

Figure 1

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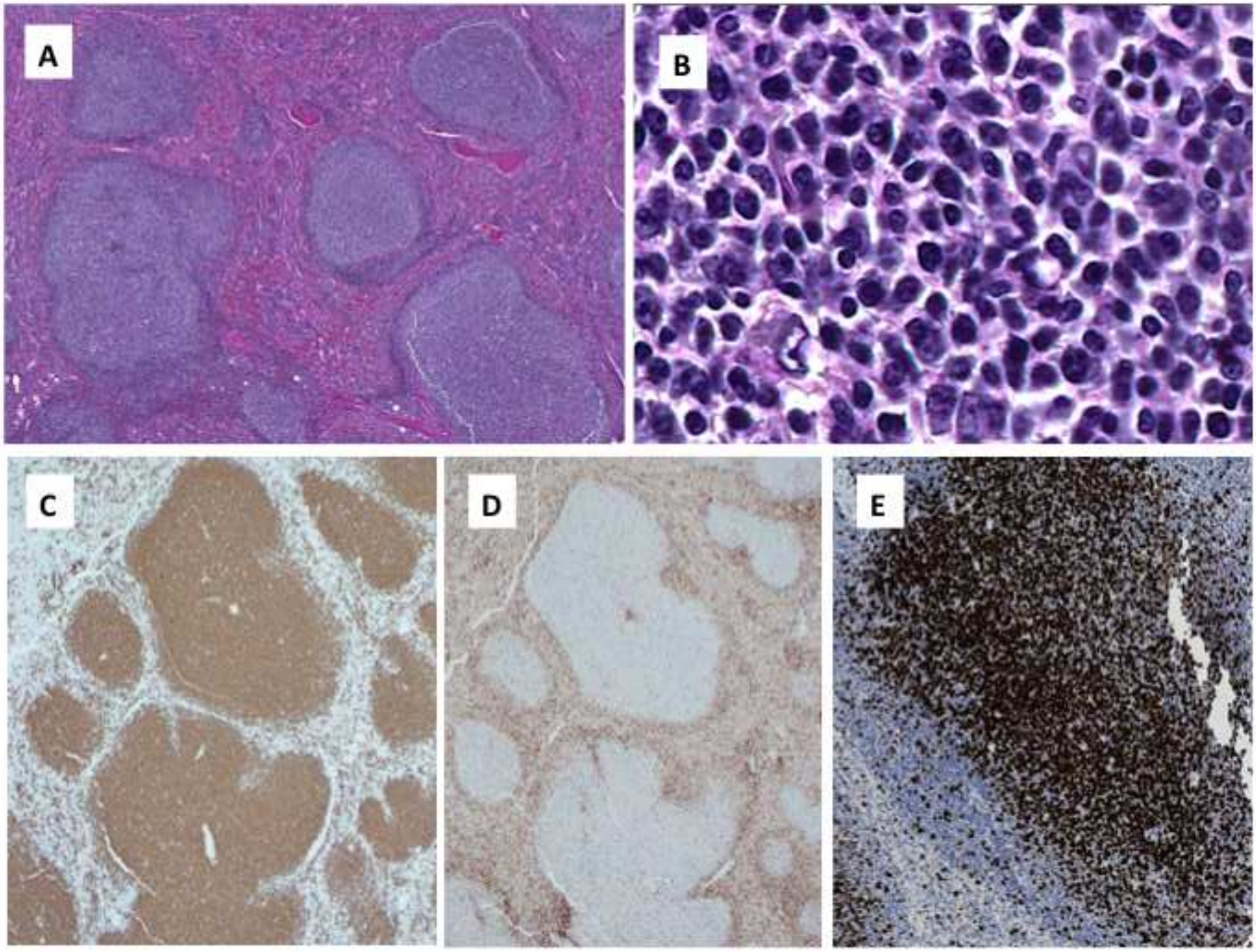

Figure 2

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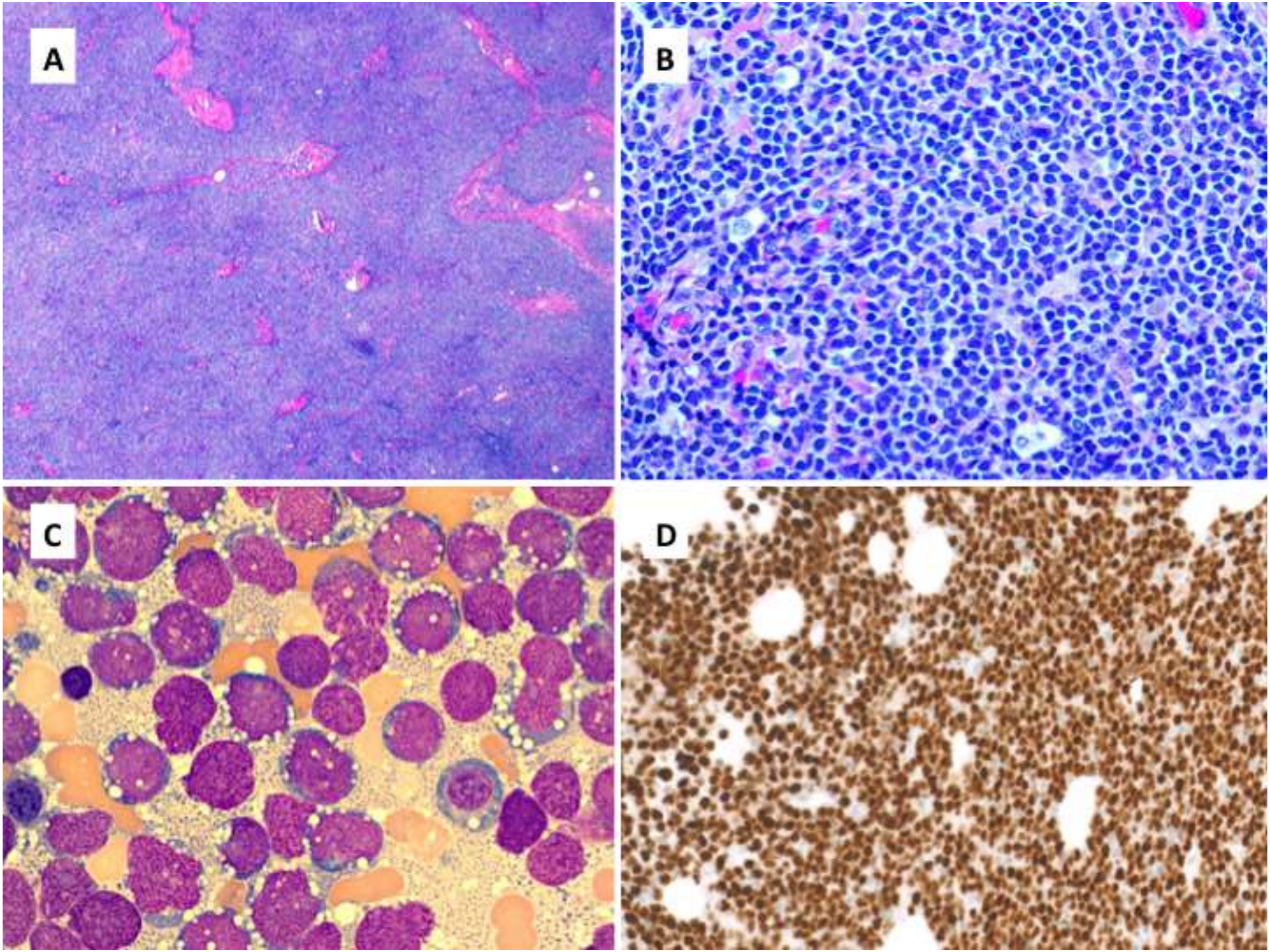

Figure 3

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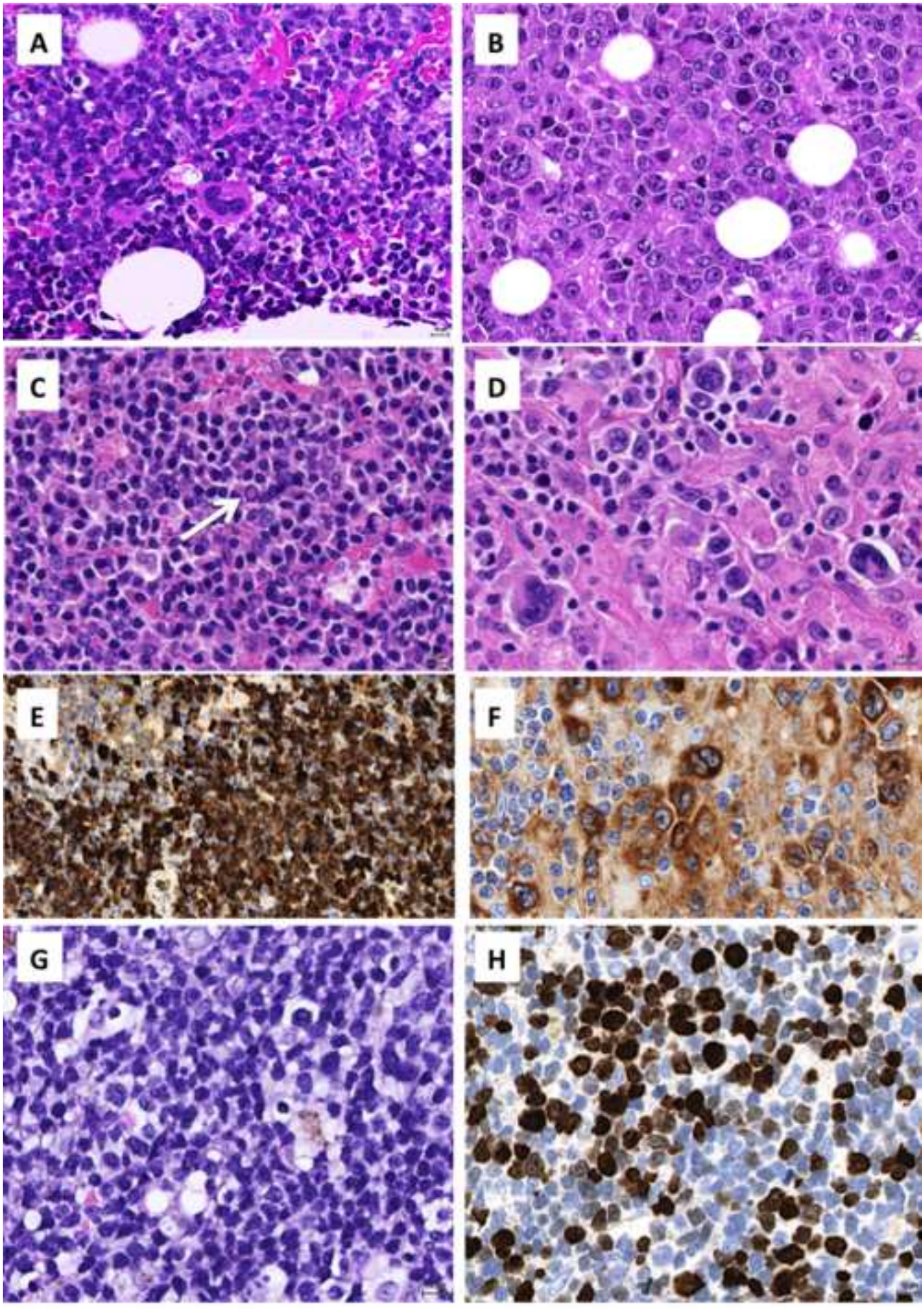

Figure 4

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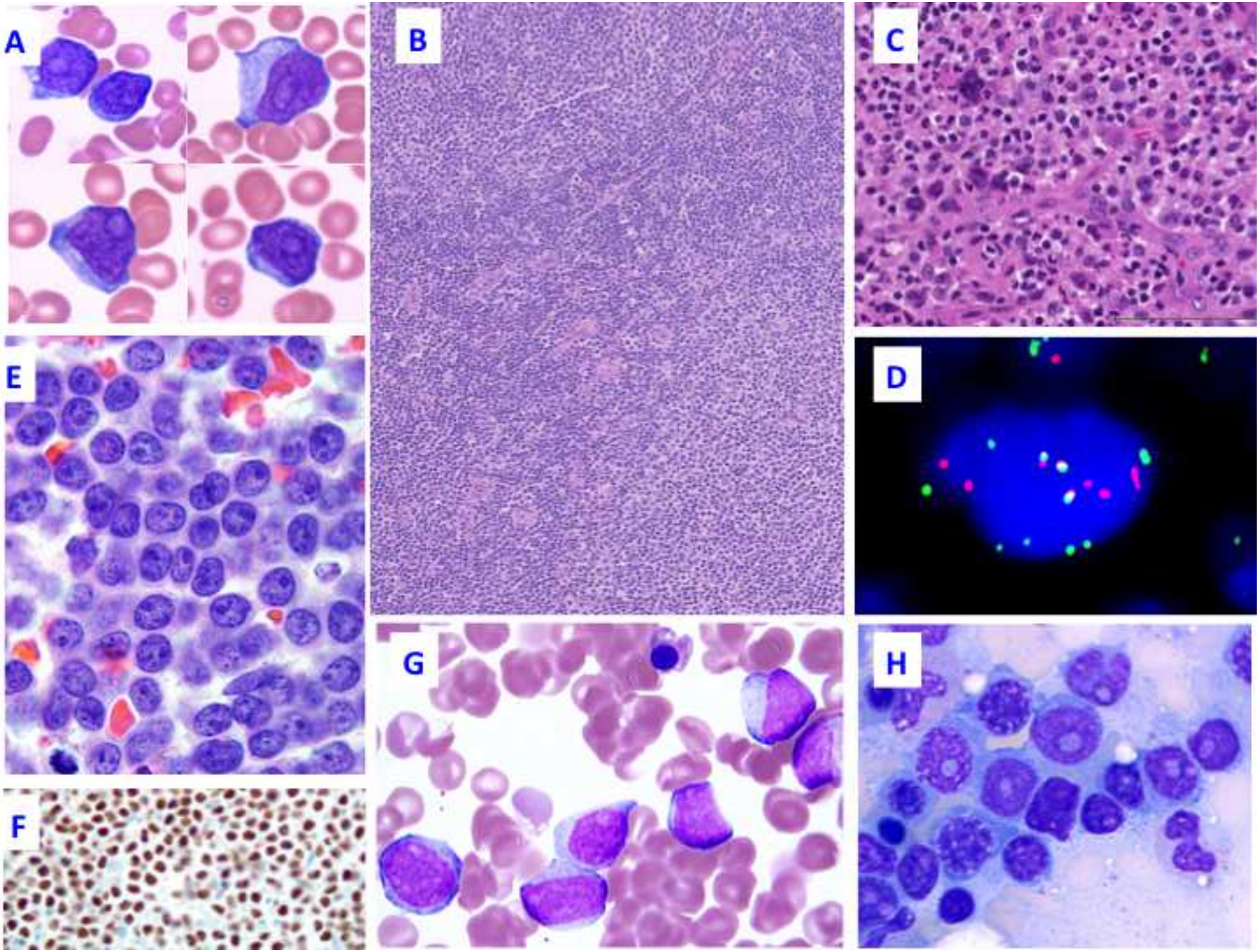

Figure 5

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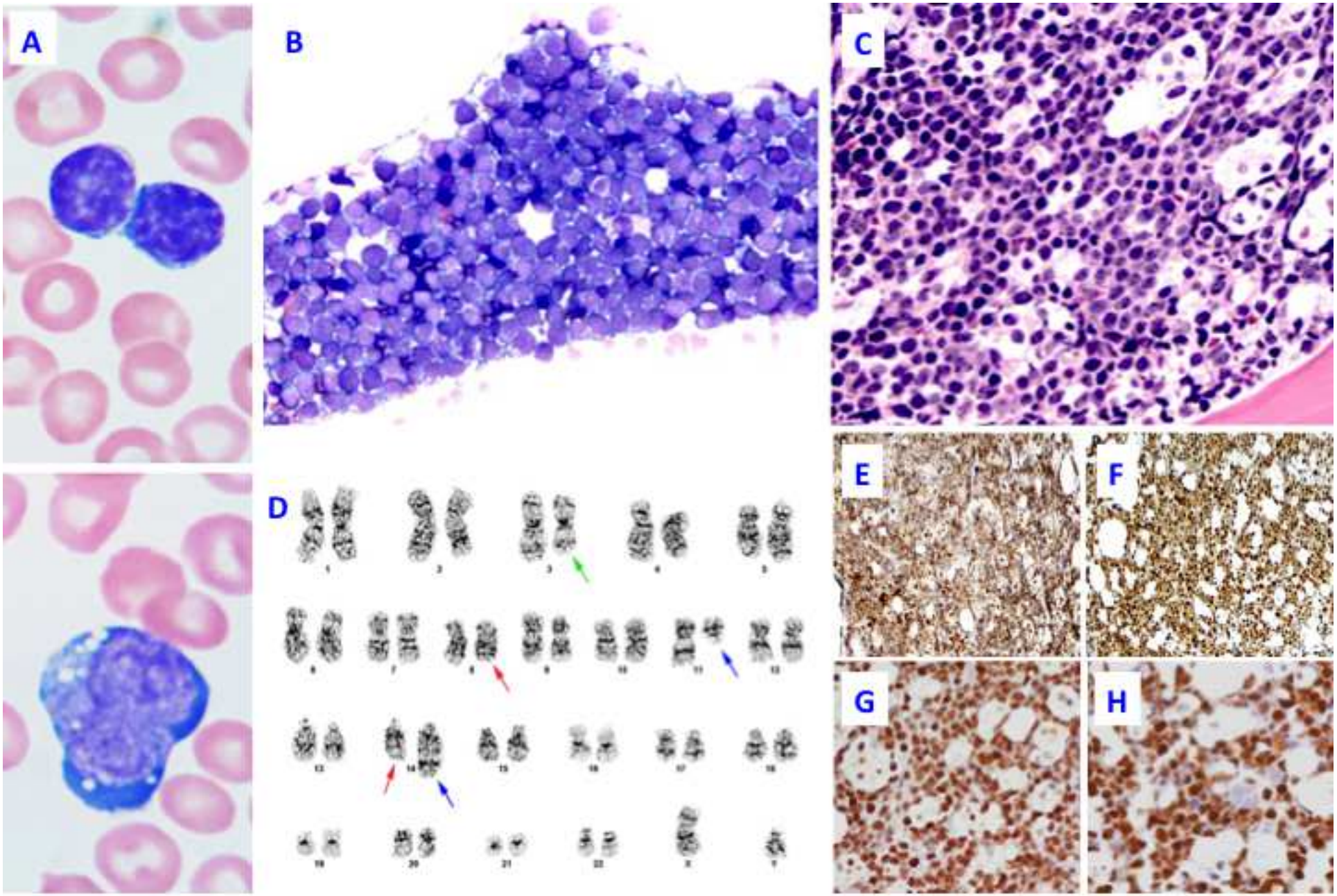

Figure 6

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