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Approach to nodal-based T-cell lymphomas

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Corresponding Author:	Laurence de Leval, MD PhD Lausanne University Hospital Lausanne, 1011 SWITZERLAND
First Author:	Laurence de Leval, MD PhD
Order of Authors:	Laurence de Leval, MD PhD
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Approach to nodal-based T-cell lymphomas

Laurence de Leval MD PhD

Institute of Pathology, Lausanne University Hospital (CHUV) and Lausanne University, Lausanne, Switzerland

Corresponding author : Laurence de Leval

Professor Laurence de Leval, MD PhD, Institute of Pathology, University Hospital Lausanne (CHUV), 25 rue du Bugnon, CH- 1011 – Lausanne, Switzerland. Phone: +41 21 3147194. Fax: +41 21 3147205.

E-mail: Laurence.deLeval@chuv.ch

Abstract

Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of uncommon malignancies derived from mature T cells and usually characterized by an aggressive clinical course. Their clinical presentation, localization and pattern of dissemination are highly variable, but the majority of cases present as nodal diseases. The recently revised classification of lymphomas has incorporated many new molecular genetic data derived from gene expression profiling and next generation sequencing studies, which refine the definition and diagnostic criteria of several entities. Nevertheless the distinction of PTCL from various reactive conditions, and the diagnosis of PTCL subtypes remains notably challenging. Here, an updated summary of the clinico-pathologic and molecular features of the most common nodal-based PTCLs (angioimmunoblastic T-cell lymphoma and other nodal lymphomas derived from follicular T helper cells, anaplastic large cell lymphomas and peripheral T-cell lymphoma, not otherwise specified) is presented. Practical recommendations in the diagnostic approach to nodal T-cell lymphoproliferations are presented, including indications for the appropriate use and interpretation of ancillary studies. Finally, we discuss commonly encountered diagnostic problems, including pitfalls and mimics in the differential diagnosis with various reactive conditions, and the criteria that allow proper identification of distinct PTCL entities.

1 Introduction

Peripheral T-cell lymphomas (PTCLs) are diverse and overall rare malignancies with substantial geographic variation in their incidence and relative prevalence.[1, 2] In the latest WHO classification of lymphomas, more than 30 distinct types of neoplasms derived from mature T or NK cells are recognized (**Table 1**). These neoplasms can be grouped according to their usual presentation into disseminated diseases (leukemias), predominantly extra-nodal or cutaneous, or predominantly nodal lymphomas. Keeping in line with the principle of a multiparametric definition of lymphoma entities, the revised classification has incorporated novel biomarkers, molecular signatures and cancer-associated mutations derived from recent high-throughput molecular and genomic profiling studies as they refine disease definition and diagnostic criteria. [3, 4] Nevertheless, proper identification and accurate diagnosis of PTCLs often remains a challenging task, for several reasons.[5-7] Firstly, distinct disease entities may encompass a wide spectrum in terms of cellular composition, morphological features and immunophenotype, secondly there is marked overlap of certain features between different diseases, and not all diseases are associated to specific mutations. Third, a variety of reactive T-cell lymphoproliferations may be mistaken for malignant conditions. Moreover, given the overall low prevalence of PTCLs, most pathologists have limited exposure and experience for confidently diagnosing these diseases.

The focus of this paper is to provide a comprehensive review on the approach to nodal-based PTCL (**Table 1**). PTCL entities primarily involving lymph nodes represent the most prevalent PTCL subtypes and account for the majority of PTCL diagnoses. Angioimmunoblastic T-cell lymphoma and the lesser common other lymphomas of follicular helper T cell derivation, namely follicular T-cell lymphoma and nodal PTCL with TFH phenotype represent the most prevalent group, followed by peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and anaplastic large cell lymphomas, anaplastic lymphoma kinase (ALK)-positive and ALK-negative.[2, 4, 8, 9] In addition, lymph nodes may be secondarily involved by T-cell leukemias (ATLL and T-PLL), or cutaneous or extranodal PTCLs. Among the latter, mycosis fungoides, primary cutaneous ALCL, NKTCL and primary intestinal T-cell lymphomas not uncommonly disseminate to lymph nodes. Conversely, indolent leukemias, HSTL, subcutaneous panniculitis-like T-cell lymphoma and other rare types of primary cutaneous T-cell lymphomas usually spare lymph nodes.

This review contains an update on the clinico-pathologic features and diagnostic criteria of the most common nodal-based PTCLs, practical recommendations for the diagnostic approach including indications on the appropriate use and interpretation of ancillary studies, and a discussion of commonly encountered diagnostic problems.

2 Pathological features of nodal-based PTCLs

2.1 Angioimmunoblastic T-cell lymphoma (AITL)

AITL is the most common specific type of PTCL and is more common in North America and Europe than in Asia.[9] AITL is derived from follicular helper T (TFH) cells[10] and manifests as a systemic disease in adults, usually elderly individuals. Patients present with generalized peripheral lymphadenopathy, often with extranodal involvement and systemic symptoms (fever, weight loss, skin rash, arthralgias, etc.). Immune abnormalities like polyclonal hypergammaglobulinemia and Coombs-positive hemolytic anemia, are frequent and typical of AITL, but not mandatory for the diagnosis. The median survival is <3 years, but a subset of patients experience long-term survival.[11, 12]

Histologically (for review, see [13]), lymph nodes involved by AITL often show a complete architectural effacement. Capsular and perinodal infiltration sparing the peripheral subcapsular sinus is a common characteristic (**Figure 1A**). In general, cytologic features of malignancy may not be evident in many cases. The overall cellularity may be low imparting a depleted-like appearance, and the infiltrate is polymorphous including variable proportions of neoplastic T cells, typically outnumbered by reactive small lymphocytes, histiocytes, immunoblasts, eosinophils and plasma cells (**Figure 1B**). The neoplastic lymphoid cells are usually atypical small to medium-sized, with round to oval or irregular nuclei, moderately abundant clear cytoplasm, and distinct cell membranes. The atypical clear cells tend to cluster in the vicinity of vessels and their identification is a critical hint to the diagnosis. Some cases may contain a large proportion of neoplastic cells (clear cell-rich variant) (**Figure 1C**). In other instances, the neoplastic cells display small lymphocyte morphology with little or no atypia (**Figure 1F**). Large B-cell immunoblasts sometimes resembling Hodgkin or Reed-Sternberg (HRS) cells represent a typical component of AITL; they are usually scattered, but sometimes numerous (B-cell-rich AITL). Some cases are rich in histiocytes and may even feature a vaguely granulomatous pattern (**Figure 1E**). Plasma cells may be

abundant, and some patients may even present with peripheral blood plasmacytosis. There is a marked proliferation of arborizing high endothelial venules, highlighted by a PAS stain. The proliferation of follicular dendritic cells (FDCs) is typically diffuse and dense, surrounding the small vessels, but may be minimal in some cases. Although FDC aggregates may be identified on routinely stained H&E sections, they are best demonstrated by immunostaining with CD21 or CD23.

Besides the most frequent pattern described above (type III), there are two other architectural patterns: AITL with hyperplastic follicles (type I), and AITL with depleted follicles (type II), comprising occasional regressive follicles.[14, 15] In AITL pattern I (10-15% of the cases) (**Figure 2**), there are many hyperplastic germinal centers with poorly developed or attenuated mantle zones, which are surrounded by a rim of atypical clear lymphoid cells merging into the paracortex expanded by a polymorphous infiltrate with increased vessels.[16, 17] Transitions between different patterns have been observed in consecutive biopsies, and overlapping features are sometimes seen in one biopsy which may comprise a combination of patterns.[14, 17] There is no evidence that histological pattern corresponds to earlier disease stage, and the histological patterns are thought to reflect morphologic evolution rather than clinical progression.[16] One study found a better prognosis for patients with pattern I disease, but that was based on a relatively small series of cases, which seems to have included cases of follicular PTCL in the group of pattern I AITL.[18] Given the lack of evidence for clinical significance, it is not necessary to specify the architectural pattern in diagnostic histopathological reports.

The neoplastic cells of AITL consist of mature TCRαβ CD3+CD4+CD8- T cells. Given the difficulty in identifying the neoplastic cells on standard stains, immunohistochemical staining can be very useful for that purpose, by highlighting the membrane contours and demonstrating atypical cells with enlarged cytoplasm. Reduced or absent of pan-T-cell antigen(s) (most commonly CD5 or CD7) is frequently observed. Numerous CD8+ cells are present as well, sometimes activated and enlarged. Aberrant coexpression of CD20 and/or partial expression of CD30 by the neoplastic cells is not unusual. [19, 20] The neoplastic cells also express several TFH-markers, including the CXCL13 chemokine; PD1 (CD279), ICOS and CD200 membrane receptors; and BCL6 and cMAF transcription factors.[21, 22] CD10, expressed by a small subset of normal TFH cells, is positive in 60-70% of the cases, however most often in a small fraction of the neoplastic cells.[23] Overall, PD1 and ICOS are more sensitive in identifying the neoplastic TFH cells than CXCL13 or CD10, which are conversely more specific.[22]

CD21 or CD23 have been used interchangeably to underscore FDC expansion, but may produce different extents of staining (**Figure 1B**). In pattern I AITL, FDC meshworks are in general limited to the reactive B-cell germinal centers with no or minimal expansion outside of B-cell follicles.

The large blastic cells are positive for CD20, PAX5 and CD79a, often CD30-positive, and may also sometimes coexpress CD15. They are usually but not always infected by EBV (positive for EBER and LMP-1).[24] The spectrum of B-cell-derived expansions in AITL comprises also EBV-negative large B-cell proliferations, and polytypic (or less commonly monotypic) plasma cell expansions, which may sometimes be EBV-positive as well. The importance of the associated B-cell proliferation may sometimes warrant a diagnosis of secondary diffuse large B-cell lymphoma.[25, 26]

Monoclonal or oligoclonal rearrangement of the T-cell receptor gene can be demonstrated in the vast majority of cases. In addition, a clonal or oligoclonal rearrangement of the immunoglobulin genes is also found in up to one third of patients, particularly in cases comprising an increased numbers of B cells.

Recent studies have revealed a rather homogeneous mutational landscape which recapitulates a multi-step oncogenic process. This profile typically consists of epigenetic deregulation (various and often multiple inactivating *TET2* +/- *DNMT3A* mutations, often occurring at early stages in hematopoietic progenitors, present in about 80% and 30-35% of the cases, respectively)[27, 28], and second hit mutations with a more restricted distribution.[29] The latter include a hotspot *RHOA*^{G17V} mutation encoding a dominant negative variant of the protein in up to 70% of cases, and other gain-of-function mutations targeting the T-cell receptor signaling pathway (*PLCG1*, *CD28, FYN, PIK3* components, C*ARD11, etc*.).[30-32] Mouse models have shown that *RHOA*^{G17V} induces TFH specification, autoimmunity, and promotes lymphomagenesis in the presence of *TET2* inactivation, indicating the synergistic effect of both mutations.[33-35] Cases of AITL with the *RHOA*^{G17V} mutation have classical clinico-pathological features and tend to have higher microvessel density, more FDC proliferation and a more pronounced TFH immunophenotype compared to wild-type cases, but no prognostic significance was observed.[36, 37] Various *IDH2* point mutations at the R172 residue are present in about one third of AITL cases.[38-40] *IDH2* mutations modify IDH2 enzymatic activity resulting in the production of an oncometabolite (2 hydroxyglutarate) ultimately altering DNA and histone methylation. [39, 41]AITL with *IDH2* mutations has a characteristic morphology with prominent

medium to large clear cells, and are characterized by a strong TFH phenotype, especially strong CD10 and CXCL13 expression.[42] Genomic imbalances are frequent as well; gains of chromosomes 5 and 21 are frequent especially in *IDH2*-mutated cases, and copy number losses enriched in genes regulating the PI3K-AKT-mTOR pathway are enriched in *IDH2*-wild type cases.[43] RNA fusions involving *CD28* and *ICOS* or rarely *CD28* and *CTLA4* are detected in a small subset of the patients and are mutually exclusive with CD28 mutations.[44]

2.2 Other nodal lymphomas of T follicular helper cell origin

In addition to AITL, the 2017 WHO classification of lymphomas recognized two other lymphoma entities derived from TFH cells, namely follicular T-cell lymphoma - originally considered as a variant of PTCL-NOS[45] - and nodal PTCL with a TFH phenotype.[4] In addition to a common cellular origin, these lymphomas also share with AITL some pathological and clinical features, and genetic background molecular signatures, suggesting that these entities belong to the spectrum of the same disease and supporting their classification under the same "umbrella" group.[27, 46, 47]

2.2.1 Follicular T-cell lymphoma (F-PTCL)

This rare form of TFH-derived PTCL refers to a pattern of growth related to follicular structures lacking the extrafollicular proliferation of FDC and proliferation of high endothelial venules characteristic of AITL. The clinical presenting features overlap with those of AITL.[48, 49] A subset of patients has long-term survival despite sometimes multiple relapses and the prognosis might be slightly better than that of AITL.[48, 49] F-PTCL manifests either a truly follicular pattern, mimicking follicular lymphoma (FL-like), or more commonly a pattern resembling progressive transformation of germinal centers (PTGC-like).[48, 50, 51] In FL-like PTCL, the neoplastic cells form intrafollicular aggregates sustained by a meshwork of FDC; some cases contain tumor medium-sized cells with abundant clear cytoplasm, and others consist of cells resembling centrocytes and centroblasts. In PTGC-like PTCL, the neoplastic cell burden may be low and consists of aggregates of medium-sized pale or clear atypical T cells, which are distributed within expanded mantle zones in large nodules mostly composed of small IgD+ B cells (**Figure 3**).

By immunohistochemistry the neoplastic cells are CD3+ CD4+ and usually feature a strong TFH immunophenotype, i.e. PD1+ ICOS+ CXCL13+ BCL6+ CD10 +/- CD57-/+ (**Figure 4**).[48, 52] One study found that the neoplastic cells had at least partial

expression of CD30 in 75% of their case series[52] A component of large blastic EBV-positive or -negative B cells is often identified, frequently with Reed-Sternberg-like morphology and immunophenotype (**Figure 4**).[24, 48, 52, 53]

A chromosomal translocation t(5;9)(q33;q22) involving ITK and SYK tyrosine kinases, is found in about 20% of F-PTCL, and has been reported thus far in only one case of typical AITL.[48, 54, 55] The *ITK-SYK* fusion may be detected by FISH assays, but its diagnostic value is rather limited. Although data are limited, the mutational pattern of follicular PTCL appears to overlap with that of AITL.[47]

2.2.2 Nodal peripheral T-cell lymphoma with follicular helper T-cell phenotype (TFH-PTCL)

Nodal TFH-PTCL encompasses cases without specific pathological features, but showing imprints of the T_{FH} signature and/or expression of T_{FH} markers, and/or exhibiting some characteristics of AITL (FDC expansion, increased vascularity, presence of EBV-positive B-blasts).[10, 27, 56] According to the WHO criteria, qualification for a TFH lymphoma requires the expression of at least 2 or ideally three TFH markers by the neoplastic cells, in addition to CD4 (**Figure 5**).[4] Often a combination of immunophenotypic TFH features and some AITL-like features is present, but overall the morphological features are too poorly developed to warrant a diagnosis of AITL.[56] Some cases show perifollicular involvement and may mimic marginal zone lymphomas.[57] A subset of cases may present as what was previously designated the "T-zone variant" of PTCL-NOS[58], in which there is preserved architecture with residual sometimes hyperplastic B-cell follicles, and interfollicular lymphomatous involvement. [59] Since FDC proliferation is generally considered as a typical hallmark of AITL, cases comprising some FDC expansion are better qualified as tumor-cell rich AITL, but the border between PTCL-TFH and AITL is not well delineated, likely reflecting a biological continuum.[15, 47] Indeed, *TET2, DNMT3* and *RHOA* mutations in morphologically unspecified PTCLs tend to be confined to the subgroup with a TFH immunophenotype.[27, 28, 30]

2.3 Anaplastic large cell lymphoma, ALK-positive (ALK+ ALCL)

ALK-positive ALCL represents about 7% of PTCLs. It is more common in North America than in Europe, and rare in Asia. ALK+ ALCL is usually composed of large cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, characterized by strong uniform expression of CD30 and rearrangement of *ALK*, most

commonly by a t(2;5)(p23;q35) fusing *ALK* to the nucleophosmin gene (*NPM1*).[4] NPM-ALK and other types of ALK fusion proteins resulting from alternative translocations (**Table 2**) lead to the constitutive activation of ALK-tyrosine kinase and represent the critical oncogenic driver.[60-62]

ALK+ ALCL preferentially affects children and young adults. It usually presents with lymphadenopathy, but involvement of other extranodal sites (skin, bones, soft tissues) is frequent. Most patients present with stage III or IV disease and systemic symptoms. Despite aggressive presenting features, patients generally show good response to therapy and have favorable outcomes.[63]

In lymph nodes, the neoplastic cells disseminate through the sinusoids, grow as diffuse cohesive sheets, and partially or completely obliterate the nodal tissue while possibly sparing residual reactive follicles, a pattern mimicking solid tumor metastasis. Involved lymph nodes may show fibromyxoid capsular thickening or an edematous stroma with an overall hypocellular appearance (Figure 6A). ALK+ ALCL encompasses a broad morphological spectrum, but all variants contain a variable proportion of the characteristic "hallmark cells". These cells are usually large or occasionally smaller with an eccentric kidney- or horseshoe-shaped nucleus, a prominent Golgi region which appears as a clear, more eosinophilic zone, and abundant, usually basophilic cytoplasm.[64] The classical form (common pattern) (60% of the cases) comprises sheets of large pleomorphic cells including multinucleated cells that may superficially resemble Hodgkin-Reed-Sternberg cells, admixed with usually numerous hallmark cells (**Figure 6B-C**). The mitotic rate is high and tingible body macrophages and areas of necrosis can be present. The small cell and lymphohistiocytic variants (<10% of the cases each, closely related and often admixed, almost always in the pediatric age group) are associated with a less favorable outcome and may be associated to a leukemic dissemination.[65, 66] In the small cell pattern, the neoplastic population comprises small lymphoid cells with irregular nuclei, abundant clear cytoplasm and distinct membrane borders, and fewer larger hallmark cells, which tend to cluster around vessels (**Figure 6D-E**).[67] In the lymphohistiocytic pattern, the neoplastic cells are scattered within a predominant population of reactive histiocytes. Other less common patterns include cases with sarcomatoid morphology, with a prominent neutrophilic infiltrate, or rich in giant cells, and a Hodgkin-like pattern resembling nodular sclerosis Hodgkin lymphoma. [68] A combination of two or more distinct patterns

may be seen in one lymph node, and relapses may reveal a morphology different from that seen initially.

In all cases the tumor cells are uniformly strongly positive for CD30 at the membrane and in the Golgi region, and by definition positive for ALK expression. The type of translocation determines the subcellular localization of ALK on immunostains, but the variant translocations have no clinical impact and no prognostic significance (**Figure 6F**) (**Table 2**). EMA is positive in the majority of cases. In the morphologic variants of ALCL, only the larger cells are highlighted by CD30 and EMA and in the small cell pattern the expression of ALK is usually restricted to the nucleus of the neoplastic cells. Despite a T-cell origin supported by demonstration of a monoclonal rearrangement of the T-cell receptor genes in most cases, the tumor cells often have defective expression of the TCR/CD3 complex and of many T-cell antigens; thus, many cases have an apparent "null" immunophenotype but exhibit an activated cytotoxic phenotype with expression of granzymeB, TIA-1, and/or perforin. CD3 is negative in >75% of cases, CD5 and CD7 are often lost as well. CD2 and CD4 are positive in a significant proportion of cases. CD8 is usually negative. Although usually negative for CD15, a subset of the cases may be positive for this marker. ALCL is by definition EBV-negative.

2.4 Anaplastic large cell lymphomas ALK-negative (ALK- ALCL)

ALK-negative ALCL is a systemic CD30+ large cell lymphoma with comparable morphology to classical ALK-positive ALCL but lacking ALK expression. ALK-negative ALCL is slightly less common than ALK+ ALCL and comprises 5-6% of PTCLs. It tends to occur in older individuals, with less frequent extranodal involvement. The clinical course and prognosis of patients are overall worse than for those with ALK-positive tumors, but more favorable than for PTCL-NOS patients.[69] However, stratification of ALCL cases according to age and stage in some studies have demonstrated similar prognosis independent of ALK expresssion [70], and the subgroups of ALK-negative ALCL according to chromosomal translocations appear to have distinct prognoses.[71-73]

The morphology overlaps with that of the common variant of ALK+ALCL, including the presence of hallmark cells. Although a variably abundant reactive component may be present in some cases, there is by definition no "morphologic variant" of ALK-negative ALCL, based on the lack of features to distinguish those

cases from PTCL-NOS. ALK- ALCL displays strong homogeneous CD30 expression but compared to ALK-positive ALCL, expression of T-cell antigens tends to be more preserved while the expression of cytotoxic markers and of EMA tends to be less frequent, especially in cases carrying a *DUSP22* rearrangement.[69, 71] PAX5 has been detected in rare cases, in association with the presence of extracopies of the gene.[74]

At the genetic level, about one third of the cases harbor rearrangement of the *DUSP22* locus at chromosome 6p25, which induces down-regulation of DUSP22, a dual-specificity phosphatase that inhibits TCR signalling.[75, 76] *DUSP22*-rearranged cases tend to have very classical morphology with many hallmark cells, while lacking both cytotoxic markers and EMA expression (**Figure 7**).[71]Compared to other ALCLs, these cases have unique molecular features - lack of STAT3 activation, DNA hypomethylation and an immunogenic phenotype (expression of cancer-testis antigens, reduced expression of PD-L1, high expression of CD58 and HLA class II)[77] -, and frequently harbor a hotspot *MSC*^{E116K} mutation in the *musculin* gene.[78] *TP63* rearrangements encoding fusion proteins homologous to a dominant-negative p63 isoform define another genetic subgroup of ALK-negative ALCL (8% of the cases).[79] In two studies, *DUSP22*-rearranged ALCLs were found to have a good outcome, similar to that of ALK-positive ALCLs, but this was not confirmed in a third case series which highlighted that some cases can present with high-risk clinical features and have an aggressive clinical course.[71-73] *TP63* rearrangements are associated with a very poor outcome, and cases lacking one of these translocations have an intermediate prognosis.[76] In addition, a subgroup of ALK-negative ALCLs have STAT3 activation resulting from rearrangements of other tyrosine kinase genes (*TYK2, ROS1, FRK*) and/or activating mutations of *JAK* and/or *STAT3*.[77]

2.5 Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

PTCL-NOS is a heterogeneous category including "by default" all mature T-cell neoplasms that lack the criteria to be categorized within any of the specifically defined PTCL entities. In particular, an important notion introduced in the 2017 classification is the exclusion of nodal PTCLs with a TFH phenotype, defined by the expression of at least two TFH markers.[4]

The disease nearly always affects adults.[80] Presentation is usually nodal, and simultaneous extranodal involvement is frequent. Most patients have disseminated

disease, constitutional symptoms, and sometimes blood eosinophilia. [81] A hemophagocytic syndrome, often associated with a rapidly fatal course, has been reported in a few cases. The overall outcome is poor (20-30% 5-year survival). [80]

The morphological spectrum of PTCL-NOS is extremely broad. Most commonly, there is diffuse architectural effacement, but some cases present with an interfollicular or paracortical infiltrate. The open marginal sinus often seen in AITL, is usually absent in PTCL-NOS. The cytology is typically pleomorphic. Many cases consist predominantly of medium-sized or large cells with irregular nuclei containing prominent nucleoli and many mitotic figures.[82-84]. Less commonly PTCL-NOS comprises a predominance of atypical small cells with irregular nuclei.[85] In some cases there may be cells with clear cytoplasm or Reed-Sternberg (RS)-like cells may be present. High endothelial venules can be increased. Many cases have a polymorphous cellular composition, with an admixture of reactive cells, including small lymphocytes, eosinophils, histiocytes, B cells and plasma cells. With relapse, the tumors tend to retain similar morphologic features and pattern of nodal involvement, but some cases are characterized by histologic progression with increased numbers of large cells.[86]

Pan T-cell-associated antigens (CD3, CD2, CD5, CD7) are positive, but one or several of these (most commonly CD5 or CD7, more rarely CD3 or CD2) may show reduced or absent expression. In >85% of cases the neoplastic cells express the alpha/beta T-cell receptor, and a minority cases are either of gamma/delta derivation, or negative for both (TCR-silent).[87-89] Most cases are CD4+CD8-, or less frequently CD4-CD8+, but some tumors are double negative, or more rarely positive for both antigens.[89-91] B-cell markers usually highlight few reactive B cells. In addition, a small proportion of PTCL-NOS (5% or less) express CD20 in a subset of the neoplastic cells. Expression of other B-cell markers (CD19, CD79a, PAX5) has been documented in rare cases of PTCL, NOS as well.[92-94] The presence of EBV-positive B-blasts or Reed-Sternberg-like cells and the occurrence of EBV-negative clonal or monotypic plasma cell or B-cell proliferations with plasma cell differentiation, which are common in PTCLs of TFH origin, have been described less frequently in PTCL-NOS; however some of these reports antedate the recognition of nodal PTCLs of TFH derivation, and it is uncertain whether they all represent true PTCL-NOS according to the current definition.[25, 95-97]

Conventional cytogenetics and array-based studies studies have documented many aberrations and complex patterns of imbalances. Rare recurrent translocations are

characterized. The t(6;14)(p25;q11.2) involving the *IRF4* locus, has been reported in three cases of clinically aggressive cytotoxic PTCL, and cases with *TP63* rearrangements may have a poor outcome.[79, 98]

2.5.1 Variants of PTCL-NOS

Two peculiar forms of PTCL-NOS are designated as variants, namely lymphoepithelioid lymphoma and primary EBV-positive nodal T-cell or NK-cell lymphoma.

The ***lymphoepithelioid variant of PTCL-NOS*** ("Lennert lymphoma"), is characterized by an abundant background of epithelioid histiocytes, which may obscure the neoplastic lymphoid cells and may be associated with a better prognosis than other PTCL-NOS.[99] The infiltrate is usually diffuse or less commonly interfollicular. The neoplastic cells are small slightly atypical CD8+ cytotoxic T cells.[84] Reed-Sternberg-like B cells, eosinophils and plasma cells are also commonly seen.[100]

Primary EBV-positive nodal peripheral T- or NK-cell lymphoma (**Figure 8A-E**) has been described in several recent reports from Asia.[101-103] These lymphomas tend to occur in elderly individuals with generalized lymphadenopathy, frequent liver or spleen involvement, and sometimes arising in the setting of immunodeficiency. They usually show centroblastic-like or pleomorphic morphology and lack the angiocentric pattern of extranodal NK/T-cell lymphoma. Necrosis is infrequent. These lymphomas are CD3+ CD5-/+ CD8+ with an activated cytotoxic phenotype, but usually CD56-negative. EBV is detected in the majority of tumor cells by in situ hybridization or expression of LMP-1. Most cases are of T-cell lineage and carry clonally rearranged T-cell receptor genes associated to 14q11.2 loss, the majority of cases express the alpha-beta TCR, subsets of cases are positive for gamma-delta TCR, or may be TCR-silent. A very small proportion of cases appear to be of NK cell derivation.[104] Compared to ENKTCL, nodal EBV-positive T- or NK-cell lymphomas are characterized by upregulation of PD-L1, CD2 and CD8, and downregulation of CD56, and a shorter survival was reported in some but not all studies.[104, 105] While primary nodal EBV+ PTCL is distinctively rare, the presence of EBV (usually only in a small number of cells, likely bystander B) is very frequent, in up to 50% of the cases, and was reported to correlate with decreased survival.[106]

2.5.2 Other immunophenotypic subgroups

CD30 expression. CD30 is often detected in occasional tumor cells, and can be more extensively expressed.[19, 107] In a study of 141 PTCL-NOS, more than 20% of the cases were extensively positive (in 50% or more of the tumor cells).[19]Staining extent and intensity tend to correlate, and are higher in cases with large cell morphology. Strong CD30 expression by a majority of the tumor cells is seen occasionally, but ALK expression is per definition absent. Coexpression of CD30 and CD15 has been reported in some PTCL, NOS, including a subset of cases containing Reed-Sternberg-like cells mimicking HL. The expression of CD15 appears to be indicative of a poorer prognosis.[89, 108]

Cytotoxic PTCL-NOS. A subset of PTCL-NOS, ranging from 15 to 30-40% of the cases in various series, express one or several cytotoxic granule-associated molecules (TIA and/or granzymeB and/or perforin) indicative of a resting or more commonly activated cytotoxic immunophenotype.[89, 91, 109] Cytotoxic PTCL-NOS include EBV-positive cases (see above), and a subset of EBV-negative cases.[101] While their morphologic spectrum is similar; phenotypically EBV-negative cases tend to be CD4+CD8- or CD4-CD8-, and frequently coexpress CD30. Independent of the viral association, a cytotoxic immunophenotype is in general indicative of a poor prognosis in PTCL-NOS.[109, 110] Accordingly, a molecular subgroup of PTCL-NOS defined by a cytotoxic signature was also found associated with a poorer survival.[111]

Cell-of-origin subgroups. Earlier studies have suggested that subclasses of PTCL, NOS might be delineated by their immunological profile according to the expression markers associated with Th1 (CXCR3, CCR5, CD134/OX40, CD69 T-bet) or Th2 (CCR4, CXCR4, ST2(L)) differentiation.[112-116] In line with this notion, gene expression profiling identified two subgroups of PTCL-NOS characterized by high expression of either GATA3 or TBX21 transcription factors (master regulators of Th2 and Th1 differentiation pathways, respectively).[111] These subgroups are mentioned in the 2017 WHO classification as they appear to bear clinical relevance, with GATA-3-positive PTCL-NOS cases and those with a cytotoxic phenotype found to have a worse outcome in comparison to TBX21-positive or non-cytotoxic tumors.[111, 117] PTCL-GATA3 exhibit greater genomic complexity with frequent loss or mutation of tumor suppressor genes targeting the CDKN2A/B-TP53 axis and PTEN/PI3K pathway. The PTCL-TBX21 subgroup has fewer copy number aberrations, primarily targeting cytotoxic effector genes, and is enriched in mutations of genes regulating DNA methylation. [43] A

few cases of non-cytotoxic PTCL-NOS positive for the forkhead box protein 3 (FoxP3) in the absence of human T-lymphotropic virus type 1 (HTLV1) infection have been reported; these cases have large cell morphology and may show reactivation of EBV.[118]

2.6 Nodal involvement by disseminated T-cell neoplasms

2.6.1 T-prolymphocytic leukemia (T-PLL)

T-PLL patients usually have disseminated lymphadenopathy in the context of a high-count lymphocytic leukemia with bone marrow infiltration and hepatosplenomegaly. Hence, the diagnosis is generally made on the peripheral blood. In the few instances where lymph nodes are biopsied, they are moderately enlarged by a diffuse and monotonous infiltrate of slightly enlarged medium-sized lymphocytes. Venules tend to be prominent. The cells are positive for pan T-cell antigens and usually CD4+CD8-, less commonly CD8+ or double-positive, with strong expression of TCL-1.[119]CD52 and CD7 are strongly expressed, while CD25 may be negative.[120]

2.6.2 Adult T-cell leukemia/lymphoma (ATLL)

In ATLL there is marked diversity in the clinical presentation and lymph node involvement occurs in the acute and lymphomatous forms of the disease.[121] The disease is common in areas endemic for HTLV-1 infection, but sporadic cases are increasingly encountered anywhere due to population migrations.[122] In cases with a leukemic component the diagnosis is often suggested by peripheral blood analysis showing the characteristic multilobated "floret cells". In lymph nodes, ATLL infiltrates may be focal or extensive and cytology is very diverse. Cells are usually medium to large and pleomorphic, may include anaplastic-like or large multinucleated giant cells, or show blastoid morphology. The picture may resemble AITL by featuring cells with clear cytoplasm and have an associated eosinophilic component.[123] Some cases contain large EBV+ B-cell blasts likely expanded as a result of the concomitant immune deficiency. ATLL is usually composed of CD4+CD8- T cells lacking CD7 expression, with strong coexpression of CD25+; they frequently show expression of PD1, ICOS and CCR4+, and may be CD30+ especially in cases with large cell morphology.[124] Expression of FoxP3, a marker for T_{REG} cells, is found in a subset of the cases.[125]Aberrant phenotypes include expression of CD20 or CD8, but cytotoxic molecules are not expressed.[126] Diverse genetic alterations have been reported, with recurrent mutations in genes

implicated in TCR signaling, NF-kappaB pathway, immune surveillance and trafficking.[127]

2.6.1 Mycosis fungoides/Sezary syndrome (MF/SS)

Most patients with MF have some degree of lymphadenopathy, usually in superficial lymph nodes draining the involved skin. Neoplastic involvement always occurs on a background of paracortical expansion with dermatopathic changes. Early cases show no architectural effacement and may be difficult to diagnose, requiring careful morphologic assessment to identify cellular atypia.[128] Clonality analysis is often useful in those cases to ascertain the presence of a monoclonal T-cell population. Overtly involved lymph nodes feature architectural effacement and clearly malignant features. In non-transformed cases the neoplastic cells are small to medium sized with irregular nuclei, with a CD2+CD3+CD4+CD5+ CD8- immunophenotype, often lack CD7 and express TCRalpha-beta. CD30 expression is frequent in large cell transformation (defined by >25% large cells). Cytotoxic markers are rarely expressed. In Sezary syndrome, involvement of lymph nodes appears as a dense monotonous infiltrate of cells effacing the architecture.

3 Diagnostic approach to nodal T-cell proliferations

There is a broad morphologic spectrum of PTCLs in lymph nodes, ranging from obviously atypical and malignant proliferations, to more or less atypical and polymorphous infiltrates that might raise the possibility of PTCL but pose the differential diagnosis with other lymphoma entities or reactive conditions (**Table 3**). The indication of the neoplastic nature of a T-cell infiltrate is based on morphology, aberrant T-cell phenotype (i.e. loss of expression of antigens normally expressed by T cells and/or expression of antigens normally not associated to normal T cells), and demonstration of clonality.[6] A summary of the immunophenotypic markers most frequently used and molecular tests useful in the diagnosis is presented in **Table 4**. Molecular genetic tests have markedly expanded with the new genetic discoveries of many recurrent mutations, and the importance of diagnostic molecular testing is likely to increase in the future. The hotspot variant RHOAG17V which is rather specific for AITL is particularly useful for confirming the diagnosis in difficult cases. In the diagnostic process it is also important to take into account the age of the patient (with the exception of ALK + ALCL, other PTCLs do essentially not occur in children), lymph node location, and the clinical information if available; notably the notion of

disseminated adenopathies, critically ill conditions and biological abnormalities may be clinical signposts to suggest the possibility of PTCL. Given the broad range of ATLL in lymph nodes, it is recommended that all patients with a diagnosis of PTCL undergo screening for HTLV-1 infection.[129] In the following paragraphs we will discuss commonly encountered situations raising specific diagnostic problems.

3.1 Reactive T-cell proliferations that can mimic lymphoma

Reactive lymphadenopathies with a predominantly paracortical and/or interfollicular pattern may be atypical and suggest the possibility of T-cell lymphoma. These include drug-induced lymphadenopathies in patients receiving anticonvulsant therapy, antibiotics or antiviral therapies, vaccination-induced reactions, nodular, dermatopathic or viral-induced lymphadenopathies, as well as non-specific etiologies.[130, 131, 132] In favor of a reactive immunoblastic proliferation are lack of architectural effacement, presence of a polymorphous infiltrate of reactive lymphoid and other cell types, in particular the admixture of large numbers of B-immunoblasts and small B cells, patent sinuses, and lack of FDC proliferation. Conversely, total tissue architecture obliteration, marked diminution of the B-cell follicles, the presence of cytologically atypical T cells (i.e. medium to large lymphoid cells with clear cytoplasm, or the presence of lymphoid cells with irregular nuclear contours) are suspicious of malignancy.

Drug-induced lymphadenopathy (**Figure 9**) is often multifocal in patients with a usually recent but sometimes remote history of drug intake, who may present a severe hypersensitivity reaction with multiple manifestations including also a skin rash, fever, elevated liver function tests, leukocytosis, peripheral eosinophilia, and elevated serum C-reactive protein and lactate dehydrogenase.[133, 134]

Paracortical immunoblastic reactions related to Epstein-Barr virus (EBV) infection represent one of the most classical and common mimickers of malignant lymphoproliferations. In infectious mononucleosis which comprises a paracortical expansion and EBV-positive B cells, there are also many T cells which may be atypical, with a high proportion of cytotoxic CD8+ cells. Gene rearrangement studies may also be of use, however they can show oligoclonal or even occasionally monoclonal patterns of antigen receptor gene rearrangement. [131] In systemic chronic active EBV infection, there is a polyclonal, oligoclonal or often monoclonal T- or NK-cell lymphoproliferation of variable clinical severity and the lymph nodes show variable

patterns including paracortical hyperplasia, follicular hyperplasia, focal necrosis and epithelioid microgranulomas.[135]

In the pediatric population, the autoimmune lymphoproliferative syndrome, a primary immune disorder due to mutations in the *FAS*/*FAS-L* and defective apoptosis, induces a marked paracortical expansion by a population of CD4-CD8- (double-negative) cytotoxic T cells.[136] This histological picture in lymph nodes may lead to an erroneous diagnosis of either T-cell lymphoblastic or peripheral T-cell lymphoma (PTCL), but the lymphoproliferation in ALPS is mature (TdT-negative) and polyclonal.[137] In PTCLs double negativity for CD4 and CD8 is uncommon, and clonality studies show monoclonal T-cell receptor gene rearrangements in most cases.

Necrotizing lymphohistiocytic lymphadenitis (Kikuchi's disease) comprises a paracortical expansion of activated cytotoxic T cells and histiocytes that is morphologically atypical and may be confused with PTCL.[138, 139] Unlike lymphoma, the overall lymph node architecture is preserved in Kikuchi's disease and the viable tissue will lack the diffuse monomorphism of lymphomas. The expression of myeloperoxidase in histiocytes is characteristic of Kikuchi's disease.[140] Most PTCLs are CD4+, whereas the proliferating T cells in Kikuchi's disease are essentially CD8.

The reactive expansions of TFH cells described in follicular lymphoma (with a follicular distribution and a density inversely correlated to grade) and in extranodal marginal zone lymphoma may be so prominent that they can raise the differential diagnosis of a neoplastic TFH proliferations, either F-PTCL or AITL (**Figure 10**).[22, 141]

3.2 PTCL involvement mimicking a reactive condition

The recognition of nodal involvement by PTCL can at times be difficult. There are instances where lymph node involvement is only focal or minimal. ALCL infiltrates can be confined to the sinusoids or produce only focal infiltration of lymph nodes that are otherwise reactive.[142] Careful microscopic evaluation at high magnification is critical to identify subtle infiltrates and CD30 immunostains are key to highlight clusters of strongly positive large cells (**Figure 11A-C**). Lymph nodes comprising AITL pattern I typically feature an overall reactive pattern with large germinal centers; however attentive examination shows attenuated mantle zones, perifollicular atypical clear cells often merging into a polymorphous infiltrate associated to an increased vascularity in the paracortex, and immunostains demonstrate positivity for T_{FH} markers and minimal FDC expansion (**Figure 2**). [16, 17, 126]

More commonly, an important problem is to diagnose the usual form of AITL (pattern III) as a malignant lymphoma. Cases with complete effacement of the nodal architecture and the typical histological picture are relatively straightforward to diagnose; however some cases may have preserved germinal centers or atypical clear cells may be not prominent and these cases may be misdiagnosed as reactive T-zone hyperplasia suggestive of a viral or dysimmune process. There is some also overlap between the pattern II of AITL and Castleman's disease and both diseases may contain abundant plasma cells, but the expansion of the mantle zones seen in Castleman's disease is absent in the regressed follicles of AITL, and the atypical T-cell population of AITL is absent in Castleman's disease. Cases of AITL or PTCL-NOS, consisting predominantly of small T-cells may be confused with a reactive process. The correct diagnosis can usually be established by careful morphological and immunohistological examination, and assessment of clonality is in general desirable to formally assess the diagnosis.

3.3 Peripheral T-cell lymphomas mimicking Hodgkin lymphomas

This differential diagnosis represents a frequent problem.

3.3.1 PTCL with HRS-like B cells

The presence of large B-cell blasts that may feature HRS-like morphology is a common finding in AITL and other lymphomas of TFH derivation, and has been reported in PTCL-NOS as well. In addition to morphological overlap with the neoplastic HRS cells of Hodgkin lymphoma, the bystander B-blasts in PTCLs are often EBV+, consistently positive for CD30 and PAX5, with a reduced B-cell expression programme (CD20+/-), and often show coexpression of CD15, resulting in significant immunophenotypic overlap as well. Morphological hints to considering T-cell lymphoma include prominent arborizing vasculature, FDC expansion, and cytomorphologic atypia of the T cells. Careful examination of the CD30 immunostain can be helpful because in TFH lymphomas and PTCL-NOS, expression of CD30 is often detected in the neoplastic T cells as well, whereas in classical Hodgkin lymphoma CD30 is typically mostly restricted to the RS cells.[20, 52] The clue to AITL diagnosis lies in immunohistochemistry showing expression of PD1 and other TFH markers in atypical T cells and highlighting rosettes of TFH cells around the HRS-like cells (**Figure 1E**).[5, 24, 143]

3.3.2 PTCL with HRS-like T cells

Pleomorphic cell content including cells with HRS morphology and/or partial CD30 expression are common features of PTCL-NOS.[19] In addition, rare cases of PTCL-NOS have been reported where the neoplastic cells - featuring or not HRS morphology - coexpress CD30 and CD15.[108, 144] Demonstration of a T-cell phenotype often with an aberrant profile and/or a monoclonal T-cell receptor gene rearrangement leads to the correct diagnosis.

3.3.3 Lymph node involvement by cutaneous CD30+ T-cell lymphoproliferations

Nodal involvement by cutaneous CD30+ T-cell lymphoproliferative disorders (transformed mycosis fungoides, lymphomatoid papulosis, primary cutaneous ALCL) may closely simulate nodal involvement by classical Hodgkin lymphoma, due to the presence of CD30+ HRS-like often positive for CD15, associated polymorphous cellular infiltrate with eosinophilia, and sometimes stromal sclerosis (**Figure 12**).[145, 146] These overlapping features may be the source of misdiagnosis, if the pathologist is not aware of the clinical history and the skin disease. Features more suggestive of nodal dissemination from a cutaneous T-cell lymphoproliferation include the presence of sinusoidal atypical cells, demonstration of a T-cell immunophenotype, lack of EBV and ultimately clonality studies. Dissemination of breast implant-associated ALCL to axillary lymph nodes may also, in rare instances, feature classical Hodgkin lymphoma-like features.[147]

3.4 T-cell-rich lymphoproliferations with a high content of epithelioid cells

When facing a nodal lymphoproliferation rich in T cells with a high content in epithelioid histiocytes, once the possibility of a benign granulomatous autoimmune or infectious condition is reasonably excluded, the main lymphoma entities to consider are: AITL, nodal PTCL with TFH lymphomas, the lymphoepithelioid variant of PTCL-NOS, T-cell/histiocyte-rich large B-cell lymphoma, or even classical Hodgkin lymphoma. The features of epithelioid AITL overlap with those of the lymphoepithelioid variant of PTCL-NOS in principle derived from cytotoxic CD8-positive T cells. However interestingly, a recent reappraisal of cases previously categorized as lymphoepithelioid/Lennert's lymphoma showed that they in fact represent examples of

histiocyte-rich PTCLs with a TFH immunophenotype (**Figure 5**).[59] In T-cell/histiocyte-rich large B-cell lymphoma; the large neoplastic B cells express a complete B-cell programme, are EBV-negative and lack strong CD30 expression, while the reactive T cells lack atypia and are polyclonal, and eosinophils and vascular hyperplasia are absent. Cases of AITL rich in epithelioid cells and with a high content of EBV-positive B-cell blasts may lead to an erroneous diagnosis of EBV-positive large B-cell lymphoma, particularly in the elderly, if the neoplastic T-cell component is overlooked.

3.5 Anaplastic large cell lymphomas

In view of its cohesive growth and sinusoidal involvement, ALCL must be distinguished from a metastatic solid tumor, carcinoma or melanoma. Immunohistochemistry is therefore critical for a correct diagnosis, and a panel including CD30, CD45, cytokeratin, EMA melan-A and S100 protein is often useful. However, immunohistochemistry can also be misleading as ALCL is often positive for EMA, may on occasion express cytokeratins [148, 149], and often lacks lymphoid lineage markers. Conversely, metastatic ALK-positive lung adenocarcinoma can involve lymph nodes, but lacks lymphoid lineage markers and CD30 expression.

3.5.1 Pitfalls in the diagnosis of ALK+ ALCL

ALK-positive ALCL encompasses a broad morphological spectrum, therefore in principle, all nodal lymphoproliferations comprising at even a subset of cells strongly positive for CD30, should be tested for ALK expression. This is particularly important for the proper identification of the small cell and the lymphohistiocytic variants of ALK+ ALCL where typically the hallmark cells are less numerous and may be rather small or obscured by the abundance of histiocytes. The identification of perivascular atypical “hallmark” cells is critical to prompt adequate immunostaining allowing the correct diagnosis.

ALK immunostain is usually robust, but it is strongly recommended to run an external positive control, if possible on the same glass slide. The intensity of staining may be variable, especially in cases with variant translocation, and in those cases it can be useful to confirm *ALK* rearrangement by FISH analysis.

3.5.2 ALCL versus classic Hodgkin lymphoma

Occasional cases of ALCL may have a vaguely nodular pattern and some sclerosis, mimicking nodular sclerosis HL. [68] The occasional expression of CD15 or PAX 5 in

ALCL is another confusing factor.[150] However, prominent inclusion-like nucleoli are usually not seen in ALCL, and the use of appropriate immunohistochemical markers (+/- molecular genetic studies) usually resolves morphologically challenging cases, as monoclonal T-cell receptor gene rearrangements detected in most ALCL cases are not found in HL.

Another pitfall in the differential diagnosis of PTCL is aberrant expression of T-cell antigens in the HRS cells in rare cases of cHL, mostly of the nodular sclerosis or lymphocyte depleted subtypes which may contain sheets of Reed-Sternberg cells (Figure 11D-I). [151, 152] CD4 and CD2 are most commonly expressed; coexpression of CD3, CD5, CD7 CD8 or cytotoxic markers is less common. Despite T-cell antigen expression, these cases lack monoclonal T-cell receptor gene rearrangement.

3.5.3 ALCL versus diffuse large B-cell lymphoma (DLBCL)

There is morphologic overlap between ALCL and the anaplastic variant of DLBCL, which is composed of large pleomorphic cells forming cohesive sheets and shows a sinusoidal pattern of growth. By immunophenotyping, anaplastic DLBCL is positive for CD45 and B-cell antigens (CD20 and CD79a). Many cases express CD30, but consistently lack ALK expression or *ALK* translocation.[153]

ALK-positive DLBCL is a very rare subset of DLBCL which must be distinguished from ALK-positive ALCL (Figure 6G-H). ALK+ DLBCL is an aggressive lymphoma which occurs in middle aged adults, predominantly in males, usually shows immunoblastic or plasmablastic features, and tends to infiltrate the sinusoids.[154, 155] The tumor cells have a terminally differentiated B-cell immunophenotype (CD20-, CD79a-, VS38+, CD138+), may coexpress CD4, and contain cytoplasmic IgA. They are also strongly positive for EMA but lack CD30 expression. Anti-ALK antibodies typically produce a granular cytoplasmic pattern of staining as a consequence of a t(2;17) translocation involving the clathrin gene (*CTCL*) at chromosome 17q23[156], but a few cases expressing the NPM1-ALK fusion with nuclear and cytoplasmic staining have been reported as well[157]

3.5.4 Systemic ALK-negative ALCL versus other PTCL entities

Nodal involvement by ALK-negative ALCL can be the primary manifestation of a systemic disease, or represent nodal dissemination of other forms of ALK-negative ALCL, i.e. primary cutaneous or breast implant-associated ALCLs. The dissemination of primary cutaneous ALCL to regional lymph node does not necessarily indicate an

aggressive behavior and therefore the distinction is important. Thus, involvement of a single lymph node by ALK- ALCL should always raise the possibility of nodal dissemination of a cutaneous lesion before concluding early stage systemic disease. Primary cutaneous cases, at variance with systemic ALCL, are usually EMA-negative and express the cutaneous addressin antigen. Rearrangements of *DUSP22* can be present in both, and thus are not discriminant. [158-160]The distinction ultimately relies on clinical staging. Breast implant-associated ALCL may disseminate to lymph nodes, with a sinusoidal pattern of involvement, often associated with perifollicular, interfollicular, and diffuse patterns. That possibility should considered in axillary lymph nodes involved by translocation-negative ALCL in a woman with breast implant(s).[147, 161]

ALK-negative ALCL may be difficult to distinguish from PTCL-NOS. In fact, the definitional criteria remain subject to variations in interpretation, especially the morphologic criteria used for "anaplastic" morphology may be subtle and frequently subjective. In particular, a subset of PTCL, NOS displays large-cell morphology and substantial CD30 expression, rendering their distinction from ALK- ALCL problematic.[80, 89, 108] The distinction is clinically important as CD30+ PTCL-NOS appear to have a prognosis significantly inferior to that of ALK-negative ALCL patients.[162] Although recent clinical and gene expression profiling (GEP) data support their existence as two separate disease entities,[61, 163, 164] the border between ALK- ALCL and PTCL, NOS is still imprecise. We found significant immunophenotypic overlap between ALK- ALCL and CD30+ PTCL-NOS, suggesting that CD30 expression may delineate subgroups of PTCL-NOS.[165] Although the diagnostic utility of FISH testing has not been formally examined in this setting, it is generally thought that *DUSP22*-rearranged cases should be classified as ALK- ALCL, which clarified the status of a significant proportion of cases that otherwise would have been considered difficult to classify since they are usually negative for both EMA and cytotoxic molecules.[71] However, *TP63* or *VAV1* gene rearrangements have been reported in association with both ALK-negative ALCL and PTCL-NOS.[79, 166]

In addition to PTCL-NOS, other PTCL entities may feature CD30 expression and/or anaplastic morphology. In particular, extranodal NK/T-cell lymphoma, nasal type, and type I enteropathy-associated T-cell lymphoma are frequently CD30+.[19, 107] Although uncommon, these entities may involve regional lymph nodes and enter in the differential diagnosis of ALK- ALCL.

3.6 Esthablishing a diagnosis of PTCL-NOS

As already emphasized, PTCL, NOS is a diagnosis by default, implying that other specific PTCL subtypes must be excluded. The typical grey zones at the borders with AITL on one hand, and with ALCL on the other hand, were discussed above. Most of the cases difficult to classify between AITL and PTCL-NOS, are nowadays categorized as nodal TFH lymphomas which are believed to be part of the AITL spectrum.

Another PTCL entity that may feature some characteristics reminiscent of AITL, is HTLV1-associated ATLL; thus it is important to recall that assessment for HTLV1 infection serology tumor test should be systematically performed in patients diagnosed with PTCL.

In addition to other nodal entities, extranodal PTCL entities and T-cell leukemias may involve lymph nodes. The possibility of ATLL should always be kept in mind; nodal involvement by ATLL can mimic PTCL-NOS, usually presents a CD4+ CD7- immunophenotype and is often FoxP3+/CD25+, a feature rarely encountered in PTCL-NOS. Dissemination from a primary cutaneous lymphoma should also be considered. When facing infiltration by an EBV-positive cytotoxic lymphoma, either of NK or T-cell derivation, the possibility of secondary localization of ENKTCL must be absolutely excluded clinically (**Figure 8F-G**). A subset of nodal PTCL-NOS are of γδ derivation, but in those instances the secondary localization enteropathy-associated T-cell lymphomas should be excluded, as well as involvement of mucocutaneous sites. When skin lesions are present, nodal involvement by mycosis fungoides/Sezary syndrome, usually transformed, should be ruled out.

4 Conclusion

The diagnosis of PTCL in lymph nodes relies on careful morphologic assessment complemented by immunophenotypic and molecular data. Importantly, pathological data have to be integrated in the light of clinical features, age and ethnicity, past history, site of involvement and associated symptoms, for providing a final assessment. Improved knowledge of the mutational landscape of PTCLs has provided novel diagnostic biomarkers that are helpful adjuncts for the diagnostic practice.

Figure legends

Figure 1. Morphological features of angioimmunoblastic T-cell lymphoma. A: low power view of a lymph node diffusely involved by AITL (pattern III) extending over the open peripheral sinus.; B: diffuse perivascular FDC proliferation highlighted by CD2 immunostaining; C: typical AITL morphology comprising a polymorphous infiltrate of atypical cells, inflammatory cells and an abundant vasculature; C: epithelioid variant of AITL comprising neoplastic clear cells and abundant epithelioid cells; D: AITL rich in clear cells; D: AITL composed of a monotonous population of small cells with scattered blasts.

Figure 1. AITL pattern I. A: a reactive hyperplastic follicle with an attenuated mantle zone is surrounded by a rim of neoplastic clear cells; B: higher power view of the atypical clear cells surrounding the germinal center (GC); C: CD20 stains the germinal center and scattered blasts in the paracortex; D: CD3 stains a rim of atypical cells around the germinal center merging into the paracortex; E: CD10 faintly stains the germinal center and is more brightly positive on a subset of perifollicular T cells; F: PD1 highlights the rim of atypical clear cells.

Figure 3. Follicular PTCL with a PTGC-like pattern. A: panoramic view showing large nodules comprising small lymphoid cells interrupted by aggregates of paler cells; B: high power view of the cellular aggregates of neoplastic cells which are medium sized with irregular nuclei and pale cytoplasm; C: CD20 stains the small cells in a nodular pattern and with a "moth-eaten" pattern; D: IgD stains the small B cells that correspond to mantle cells; E: CD21 stains a dense FDC meshwork underlying the allege nodules; F: CD4 stains the aggregates of neoplastic pale cells.

Figure 4. Neoplastic cells and B-cell blasts in follicular PTCL. A: aggregates of pale neoplastic cells admixed to scattered large blastic cells; B-C: the blastic cells are negative for CD20 (B) and weakly positive for PAX5 (C); D-F: the neoplastic cells are strongly positive for several TFH markers, ICOS (D), PD1 (E) and CD10 (F); G: CD30 stains strongly the large blastic cells but also a large subset of the T cells; H: the large blastic cells are positive for EBV (LMP-1 immnuohistochemistry); I: some of the blasts coexpress CD15.

Figure 5. Nodal PTCL with TFH phenotype. A: the nodal architecture is effaced by a a diffuse lymphoproliferation associated to abundant histiocytes and microgranulomas (Lennert pattern); B: the lymphoid infiltrate consists of atypical

pleomorphic medium to large cells ; C: CD4 stains the majority of lymphoid cells and the histiocytes; D: CD8 stains a small subset of reactive cells including activated large cells; E: many cells are PD1-positive; F: a significant subset of atypical cells show cytoplasmic staining for CXCL13; F: the majority of cells are positive for ICOS. There was no FDC expansion, no B-cell blast component and EBV was not detected.

Figure 6. ALK-positive large cell lymphomas. A-F: ALK+ ALCL. capsular sclerosis and a cohesive growth pattern with residual germinal centers; B: case rich in giant multinucleated cells; C: case composed of large cohesive cells with vesicular nuclei and multiple nucleoli; D-E: small cell variant with perivascular clustering of larger cells immunostained for CD30 (E); F: ALK immunostaining in a case with the t(2;5) translocation; .G-H: ALK+ DLBCL. G: diffuse lymphoma composed of large cells with immunoblastic to plasmablastic morphology; H: ALK immunostaining produces a cytoplasmic granular and membrane staining typical of *ALK-CTCL* rearrangement.

Figure 7. ALK-negative ALCL with *DUSP22* rearrangement. A: typical ALCL morphology with many hallmark cells; B-G: immunostains show very faint CD3 expression (B), positivity for CD4 (C), CD30 (D) and CD5 (E), lack of expression of EMA (F) and perforin (G); H: *DUSP22* rearrangement demonstrated by FISH using a break apart probe.

Figure 8. EBV-positive nodal NK cell lymphoma versus nodal involvement by extranodal NK/T-cell lymphoma. A-E: EBV-positive nodal NK cell lymphoma. A: the lymph node architecture is diffusely effaced by an infiltrate of medium to large cells with pale cytoplasm; B-E: the lymphoma cells are CD3+ (B), CD5-negative (C), are positive for EBV as shown by in situ hybridization for EBERs (D), and show an activated cytotoyic phenotype (granzyme B, E); CD56 was negative and by genotyping the cells were of NK cell lineage. F-G: nodal involvement by extranodal NK/T-cell lymphoma (ENKTCL). F: focal atypical lymph node infiltrate of medium-sized lymphoid cells showing brisk mitotic activity in a patient recently diagnosed with multiple visceral localizations of EBV-associated ENKTCL; G: immunostaining for TCRdelta demonstrated the Tγδ lieage of the neoplastic cells in this case. The atypical cells were also EBV-positive.

Figure 9. Atypical reactive lymphadenopathy. Voluminous lymph node in a young adult with disseminated lymhpadenopathy, splenomegaly, a cutaneous rash and general symptoms, clinically suspicious for lymphoma. A: low power view shows architectural effacement while the capsule is preserved; B-C: panoramic views of immunostains for

CD20 (B) and CD5 (C) show a preserved architecture with markedly expanded paracortex; D-E: the paracortex comprises prominent veinules, numerous acceossory cells and a lymphoid infiltrate including many large blastic cells; F: many blastic cells are CD30+; G: S100 underlines many interdigitated and Langerhans cells; H: a minority of the lymphoid cells are CD8+. This case was sent for review after a suspicion of PTCL-NOS was raised. No clonal TR rearrangement was demonstrated. Clinical history revealed recent amoxicilline intake and it was concluded to a drug-indiced reaction.

Figure 10. Expansion of reactive TFH cells in a follicular lymphoma. Lymph node in a patient with history of follicular lymphoma. A-B: histological features on HE stains were consistent with follicular lymphoma; C: CD21 confirmed a follicular pattern; D-E: CD20 stained the periphery of the follicles (D) while the majority of cells in the nodules were CD4+ (E), a pattern that may suggest follicular T-cell lymphoma; F-G: PD1 stained the majority of T cells. TR gene rearrangements were polyclonal.

Figure 11. Ptifalls in the diagnosis of ALCL. A-C: focal sinusal involvement in ALK+ ALCL may be subtle on morphology alone, and is demonstrated by immunohistochemistry showing positivity of the large cells for perforin (B) and ALK (C). D-I: Nodular sclerosis Hodgkin lymphoma with aberrant expression of T-cell antigens. D: this case comprised sheets of sheets of HRS cells ; E-I : by immunohistochemistry the neoplastic cells were strongly positive for CD30 (E), weakly positive for PAX5 (F), and coexpressed CD5 (G), CD2 (H) and CD4 (I):.

Figure 12. Lymph node involvement by transformed mycosis fungoides (MF). A-B: the lymph node showed irregular fibrosis and a diffuse or vaguely nodular polymorphous infiltrate comprising many large lymphoid cells, including some HRS-like cells, and eosinophils. D-G: on immunostains, CD30 strongly stained many large cells (D) and there was coexpression of CD15 in a subset of the largest cells (E), CD4 stained the large atypical cells and many cells in the background (F) while CD3 was negative in the large cells (G). The same TR clone was demonstrated in the lymph node and in the skin lesion.

Table 1: WHO classification of mature T-cell and NK-cell neoplasms (adapted from[4] (* designates provisional entities)

Disseminated/leukemic

T-cell prolymphocytic leukaemia

T-cell large granular lymphocytic leukaemia

Chronic lymphoproliferative disorder of NK cells*

Aggressive NK-cell leukemia

Systemic EBV-positive T-cell lymphoproliferative disease of childhood

Chronic active EBV infection of T- and NK-cell type, systemic form

Adult T-cell leukaemia/lymphoma

Extranodal

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma

Intestinal T-cell lymphoma, not otherwise specified

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract*

Hepatosplenic T-cell lymphoma

Breast implant-associated anaplastic large-cell lymphoma*

Cutaneous

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

Primary cutaneous anaplastic large cell lymphoma

Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

Primary cutaneous γδ T-cell lymphoma

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*

Primary cutaneous acral CD8+ T-cell lymphoma*

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*

Hydroa vacciniforme-like lymphoproliferative disorder

Severe mosquito bite allergy

Nodal

Peripheral T-cell lymphoma, not otherwise specified

Angioimmunoblastic T-cell lymphoma (AITL)

Follicular T-cell lymphoma

Nodal peripheral T-cell lymphoma with T follicular helper phenotype

Anaplastic large-cell lymphoma, ALK-positive

Anaplastic large-cell lymphoma, ALK-negative

ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; NK, natural killer.

Table 2. Translocations and fusion proteins in ALK-positive anaplastic large cell lymphoma[167-169]

Translocation	Partner gene	Frequency	ALK staining pattern
t(2;5)(p23;q35)	Nucleophosmin (*NPM1*)	80%	Cytoplasmic and nuclear
t(1;2)(q25;p23)	Tropomyosin 3 (*TPM3*)	10-15%	Cytoplasmic with peripheral reinforcement
inv (2)(p23q35)	Pur H gene (*ATIC)*	1%	Cytoplasmic
t(2;3)(p23;q12.2)	TRK fused gene (*TFG*)	<1%	Cytoplasmic
t(2;17)(p23;q23)	Clathrin heavy chain (*CLTC*)	<1%	Cytoplasmic, granular
t(2;22)(p23;q11.2)	Myosin heavy chain (*MYH9*)	<1%	Cytoplasmic
t(2;17)(p23;q25)	Ring finger protein 213 (*RNF213/ALO17*)	<1%	Cytoplasmic
t(2;19)(p23;p13.1)	Tropomyosin 4 (*TPM4*)	<1%	Cytoplasmic
t(2;X)(p23;q11-12)	Moesin (*MSN*)	<1%	Membrane-associated
t(2;9)(p23;q33)	TNF receptor associated factor 1 (*TRAF1*)	<1%	Cytoplasmic Lymphohistiocytic morphology
t(2 ;11)(p23;qR3)	Eukaryotic translation elongation factor 1 (*EEFIG*)	<1%	Cytoplasmic
t(2 ;8)(p23;q22)	Poly (A) binding protein cytoplasmic 1 (*PABCP1*)	<1%	Cytoplasmic

Table 3. Morphologic patterns in nodal PTCLs and their differential diagnosis

Compartment	Pattern	PTCL entities	Differential diagnosis
Sinus	Sinusoidal involvement	ALCLs	Metastatic caricnoma, melanoma Sinus histiocytosis Anaplastic DLBCL
	Open sinus with perinodal infiltrate	AITL	Not typical of other PTCL entities and not a feature of reactive LN
Vessels	Hyperplastic high endothelial veinules	AITL PTCL-NOS	Reactive LN
	Perivascular large atpyical cells	ALCL variants	
	Angiocentric	ENKTCL	Lymphomatoid granulomatosis
Follicles	Perifollicular	AITL pattern I	Reactive LN Marginal zone lymphomas
	Follicular	F-PTCL	Reactive follicular hyperplasia Follicular lymphoma
	PTGC	F-PTCL	Reactive LN with PTGC NLPHL LR-cHL
Paracortex	Paracortical expansion	AITL TFH-PTCL PTCL-NOS ATLL T-PLL MF/SS	Reactive LN: drug reaction, viral infections (EBV), non-specific paracortical hyperplasia Hodgkin lymphomas
All	Diffuse	All	Depending on cytologic composition, Hodgkin lymphomas, B-cell lymphomas ...
Cytology	**Cell type(s)**		
Monomorphic	Large cells	ALCL PTCL-NOS	DLBCL Plasmablastic lymphomas

	Medium-sized cells, +/- clear cytoplasm	ALCL small cell variant PTCL-NOS EBV+ PTCL-NOS	Marginal zone and other small B-cell lymphomas
	Small cells	T-PLL PTCL-NOS	Small B-cell lymphomas
Polymorphous	Atypical lymphoid cells, histiocytes, small lymphocytes, plasma cells, eosinophils	AITL TFH-PTCL PTCL-NOS ATLL	Reactive LN
	Histiocyte cell rich	AITL TFH-PTCL PTCL-NOS, lymphoepitheioid variant (Lennert) ALK+ ALCL, histiocyte-rich	T-cell/histiocyte rich large B-cell lymphoma Granulomatous lymphadenites Hodgkin lymphomas
	With HRS cells	AITL TFH PTCL PTCL-NOS ATLL	Classical or nodular lymphocyte predominance Hodgkin lymphomas

Table 4. Summary of immunophenotypic markers and genetic molecular studies useful for the diagnosis of nodal T-cell lymphoproliferations.

Antigens	Diagnostic utility	Comments and pitfalls
Pan-T-cell antigens CD2, CD3, CD5, CD7, CD43	Identification of reactive and neoplastic T-cell (or NK) populations Loss of T-cell antigen expression is a phenotypic marker of clonality	Extensive loss of T-cell antigens and possibly «null» immunophenotype in ALCL
CD4 and CD8	Characterization of T-cell proliferations according to the CD4+CD8- or CD4-CD8+ lineages. An admixture of CD4+ and CD8+ is more characteristic of reactive lymphoproliferations	Double positive or double negative expression may indicate: immature T-cells (TdT+), γδ or NK cells, or aberrant phenotype in mature T cells, usually indicative of malignancy
TCRbeta and TCRdelta chains	Identification of TCRαβ versus TCRγδ T cells	Most nodal PTCLs derive from TCRαβ T cells PTCL may show TCR downregulation, double negative or double positive TCRβ and TCRδ phenotypes
Cytotoxic molecules: TIA-1, perforin, granzyme B	Identification of a resting (TIA1+) or activated (perforin+ or granzyme B+) cytotoxic phenotype ALCL and small proportion of PTCLs	Many reactive cytotoxic cells may be present in non-cytotoxic lymphomas (AITL for example) A cytotoxic phenotype in PTCL-NOS is indicateve of poorer prognosis
TFH markers: PD1, ICOS, CXCL13, CD10, CD200, BCL6, cMAF	TFH immunophenotype defined by the expression of at least 2 TFH markers in CD4+ cells	None of the TFH markers is in isolation sensitive or specific for TFH phenotype Significant expression implies a level of positivity similar to that of reactive germinal center-associated TFH cells
FDC markers: CD21, CD23	Expansion of FDC characteristic of AITL;	AITL pattern I has no FDC expansion

	demontration of follicular pattern in F-PTCL	
B-cell markers: CD20, CD79a, PAX5	Identification of a B-cell component or microenvironment in TFH lymphomas Abundant B cells in association with a T-cell lymphoproliferation favors a reactive over malignant process	Some PTCLs may coexpress CD20 and/or other B-cell antigens PAX5 positivity in a subset of ALCLs
CD30	Activation non lineage-specific marker Strong expression in ALCLs, heterogeneous expression in a proportion of cases in many PTCL entities, usually in a subset of the cells	Only scattered cells may be positive in small cell and histiocyte rich variants of ALK+ ALCL Differential diagnosis of CD30+ HRS-like cells in AITL and PTCL-NOS, versus Hodgkin lymphoma
CD15	May be expressed in ALCL	Coexpression of CD30 and CD15 otherwise typical of classic Hodgkin lymphoma, in a subset of PTCL-NOS and in bystander HRS B cells in PTCLs
ALK	ALK+ ALCL	ALK expression in a subset of plasmablastic DLBCLs, some carcinomas and inflammatory myofibroblastic tumors
CD138, kappa, lambda	Plasma cells May be abundant in TFH lymphomas	Monotypic or even monoclonal plasma cells in some TFH lymphomas
EBER, LMP-1	EBV-asociated lymphomas EBV-positive bystander B cells in TFH lymphomas, PTCL-NOS, ATLL	
CD56	Cytotoxic and NK cell lymphomas	
Transcription factors: TBX21, GATA3, FOXP3	Subsets of TH1 (TBX21+) and TH2 (GATA3+) PTCL-NOS	Broad range of expression of GATA3 in non-hematological malignancies and other lymphomas, including ALCLs

	FOXP3 (Treg) expression in a subset of ATLLs	
TdT	Immature (lymphoblastic) lymphoproliferations	
Antigen receptor genes rearrangement studies		
TRB and TRG	Monoclonal gene rearrangements in PTCLs NK versus T-cell derivation Confirmation of malignancies in cases with minimal involvement or when morphology and immunophenotyping are not definitively conclusive of a T-cell neoplasm	No correlation with TCRαβ versus TCRγδ phenotype Monoclonal TRB or TRG rearrangements may be detected in reactive T-cell lymphoproliferations (EBV-associated for example)
IGH, IGK	Monoclonal gene rearrangements in general indicative of a B-cell neoplasms	Monoclonal IGH or IGK rearrangements may be detected in PTCLs with a B-cell component (TFH lymphomas)
Specific genetic alterations		
DUSP22 rearrangements	Subset of ALK-negative ALCLs	Also in a subset of primary cutaneous ALCLs (and rare cases of lymphomatoid papulosis) Correlation with immunophenotype and other molecular features
TP63 rearrangements	Small subset of ALK-negative ALCLs	Also in some PTCL-NOS TP63 expression also in cases without *TP63* rearrangement
ITK-SYK fusion	Subset of F-PTCL	No prognostic significance
CD28-ICOS and *CD28-CTLA4* fusions	Subset of TFH lymphomas, rare in PTCL-NOS, cutaneous lymphomas and ATLL	
RHOAG17V	Hotspot mutation in AITL and TFH lymphomas	Other *RHOA* variants occasional in TFH lymphomas and frequent in ATLL

IDH2	Hotspot mutations at R172 residue in one third of AITLs	Correlation with clear cell morphology May be targeted by IDH2 inhibitors
TET2, *DNMT3*	Inactivating mutations, often multiple, very frequent in TFH lymphomas and less common in other PTCLs	Mutations also associated to clonal hematopoiesis and therefore not necessarily indicative of a T-cell malignancy
CD28, *PLCG1*, *CARD11*,…	Gain-of-function mutations recurrent in TFH lymphomas and ATLL, and cutaneous T-cell lymphomas	

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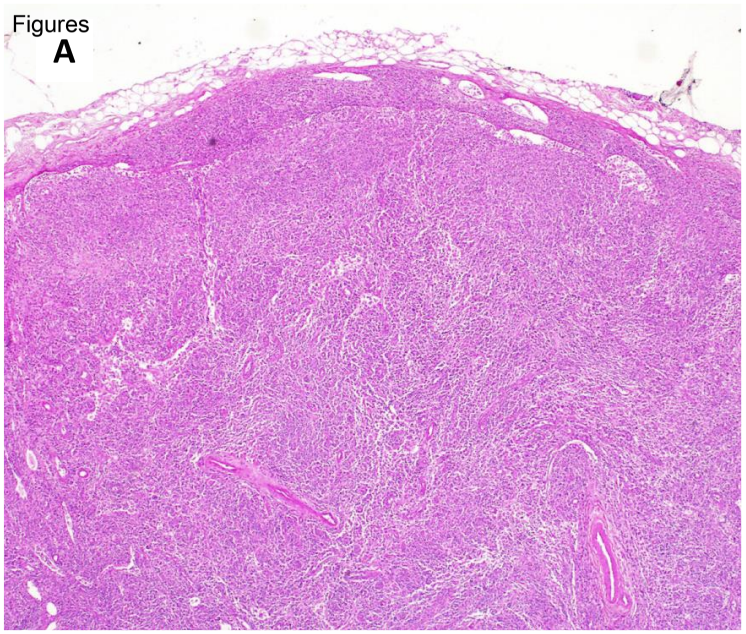
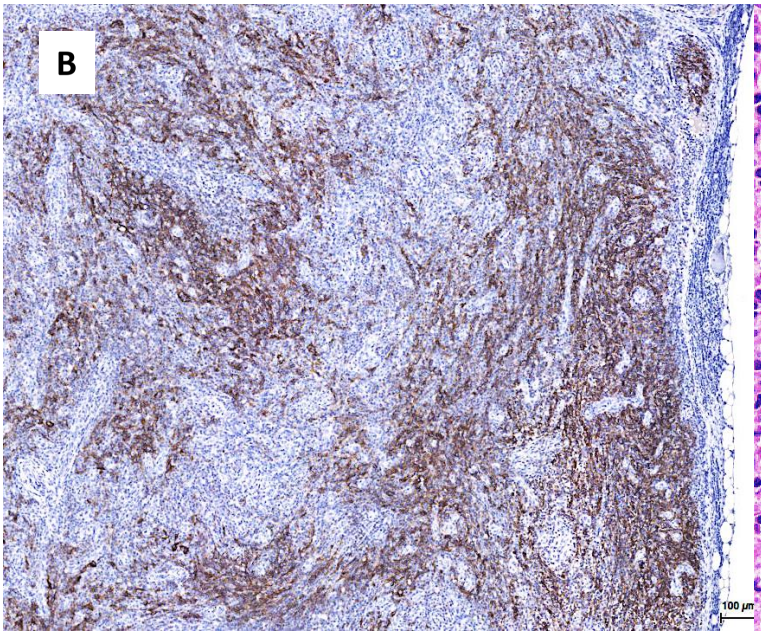
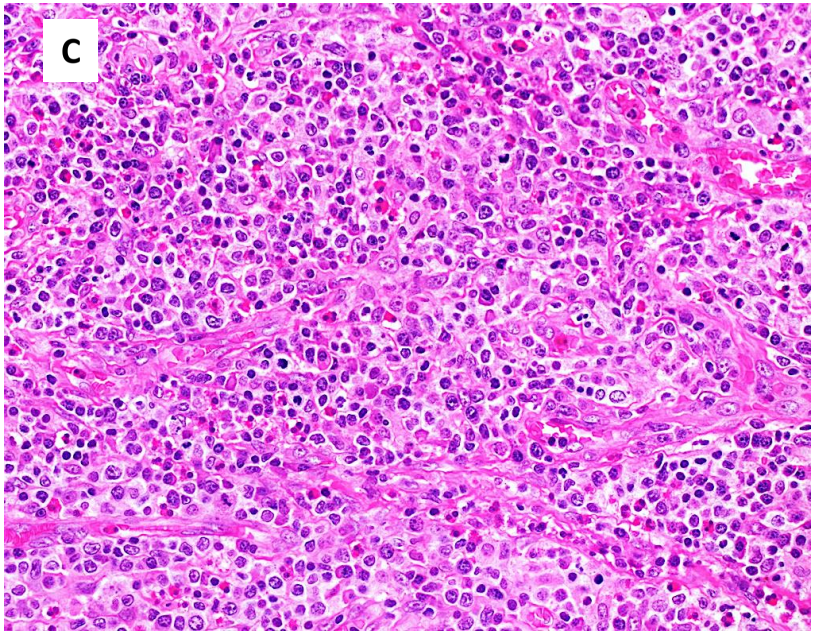
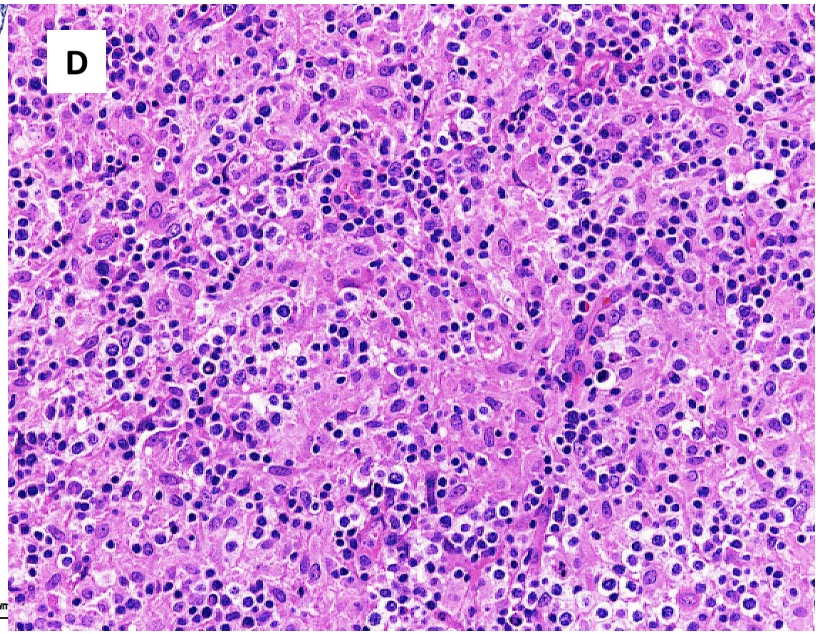
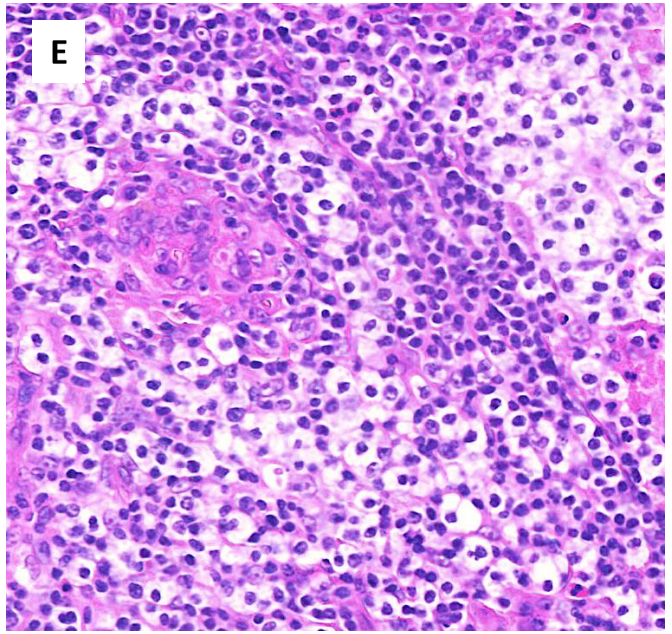
Figures

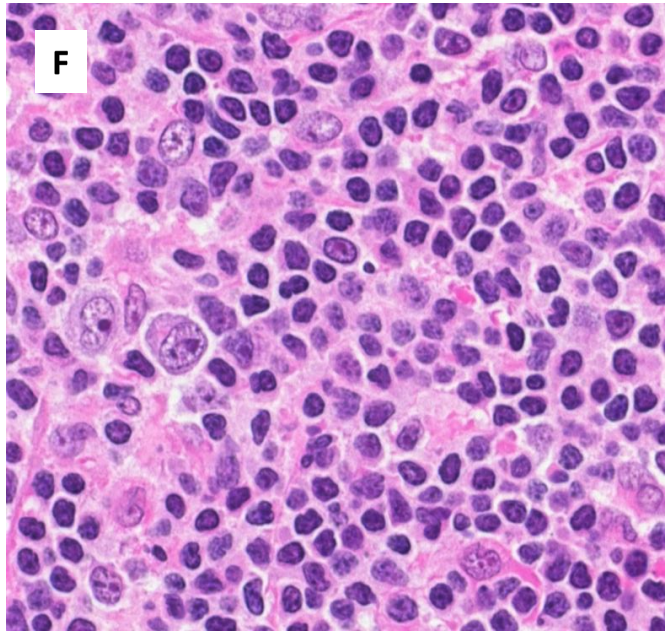


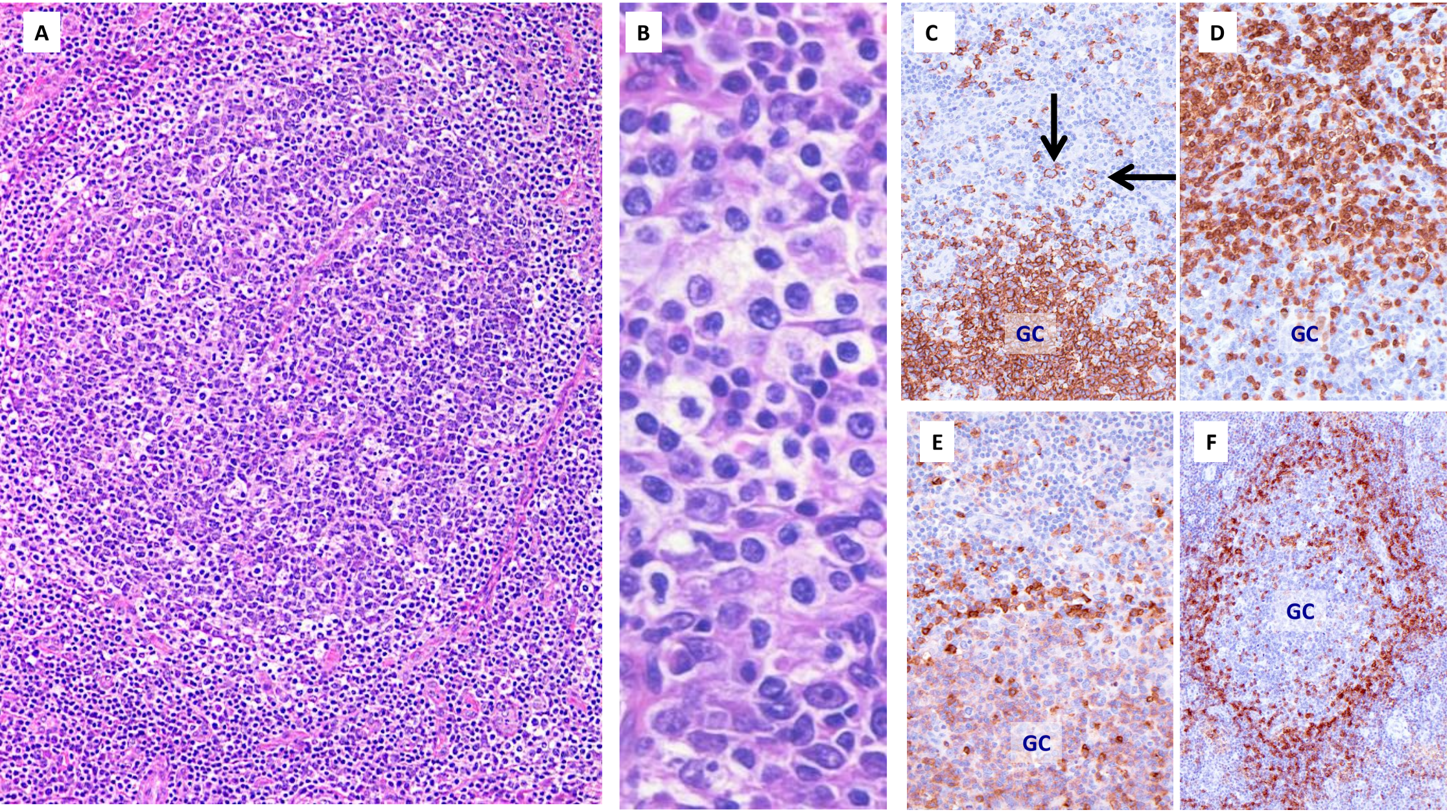








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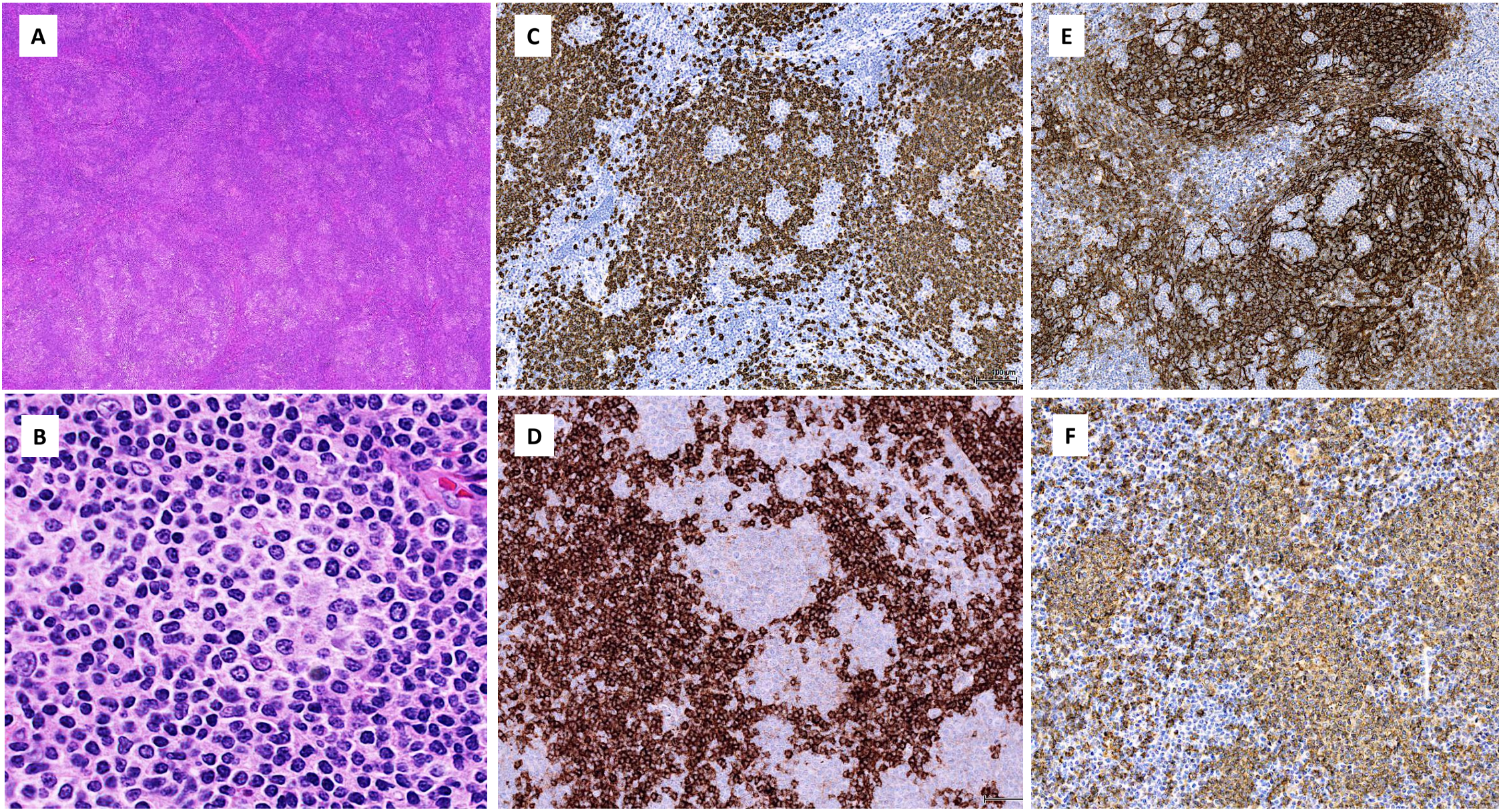
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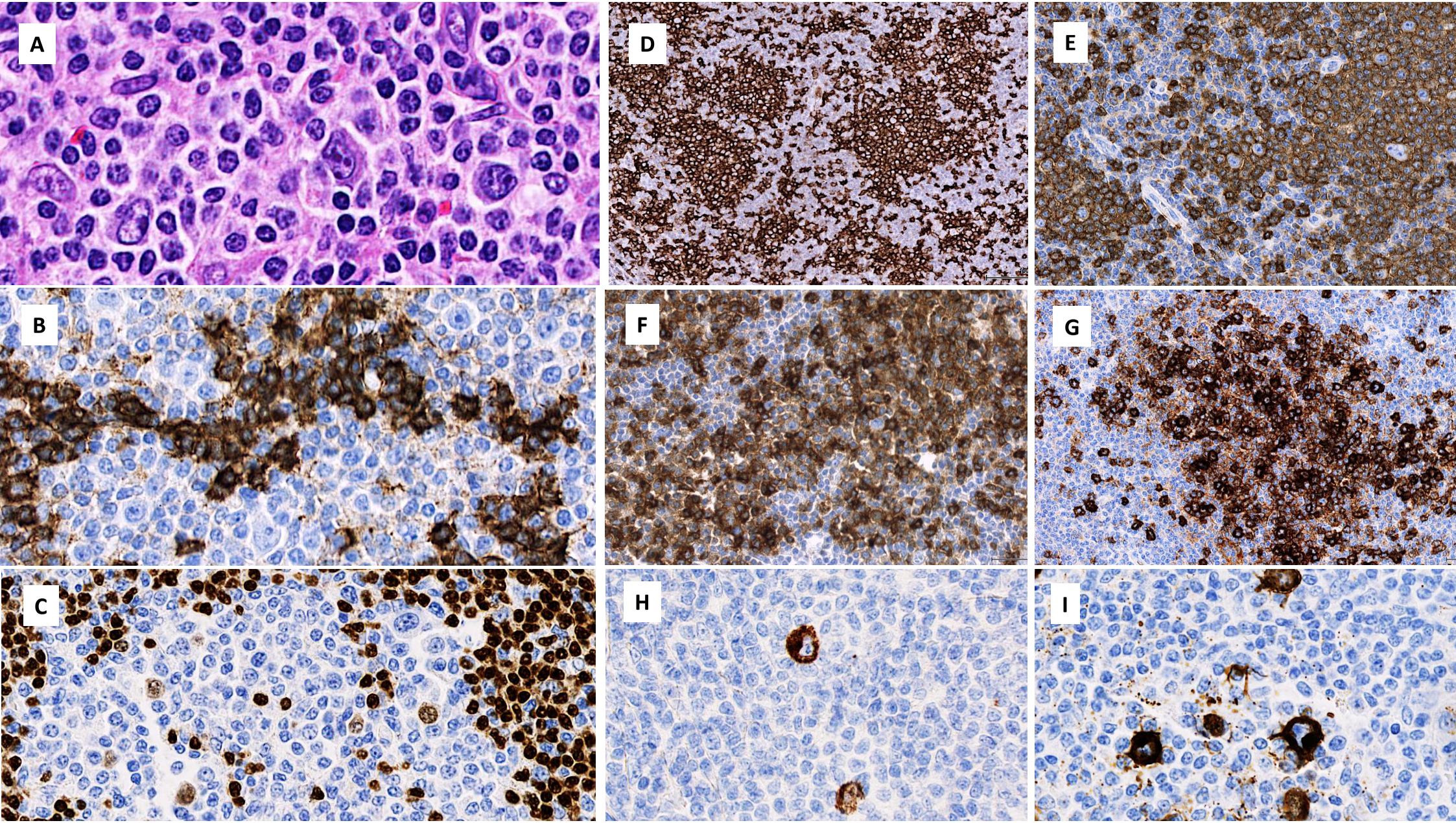
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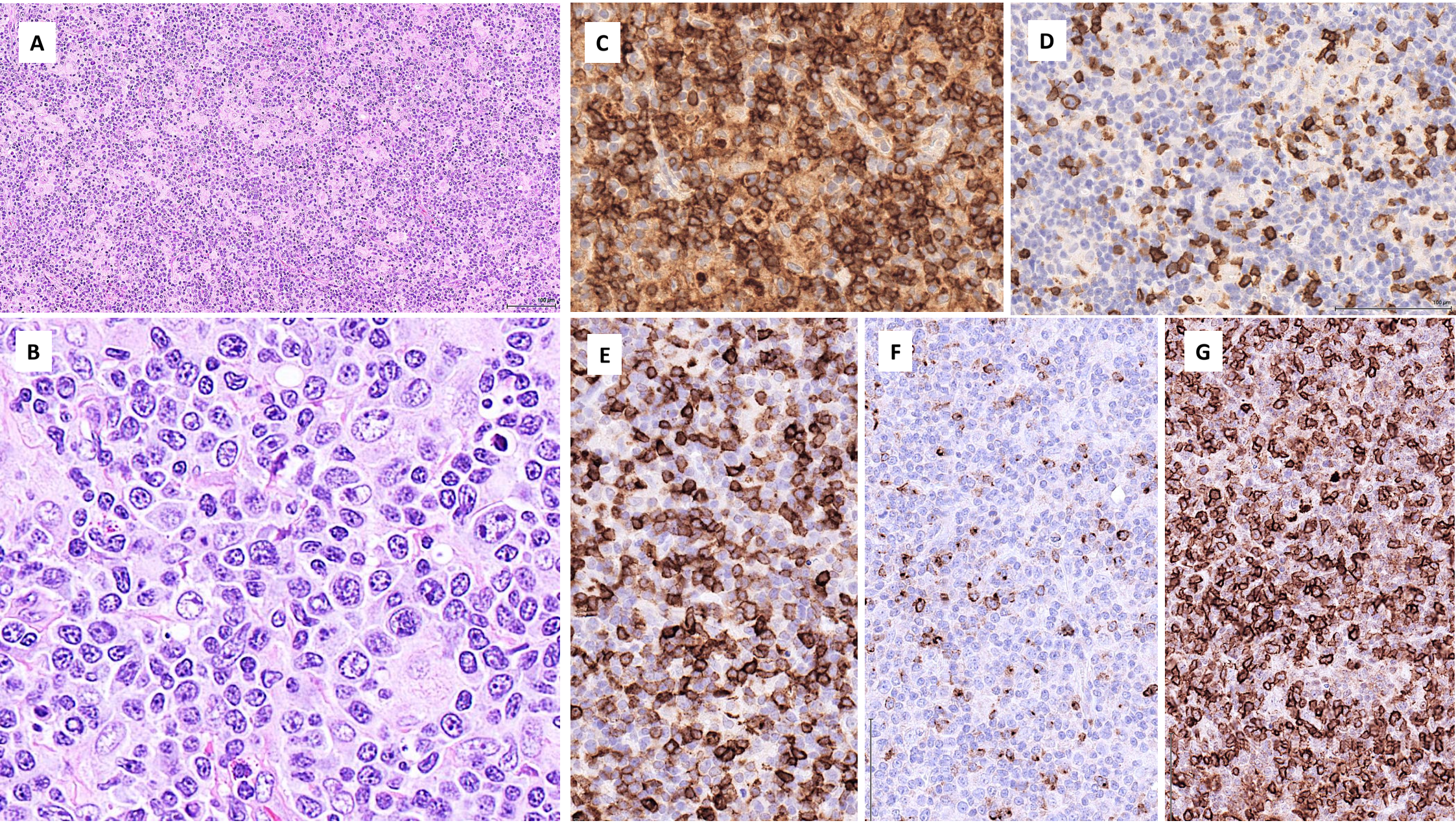
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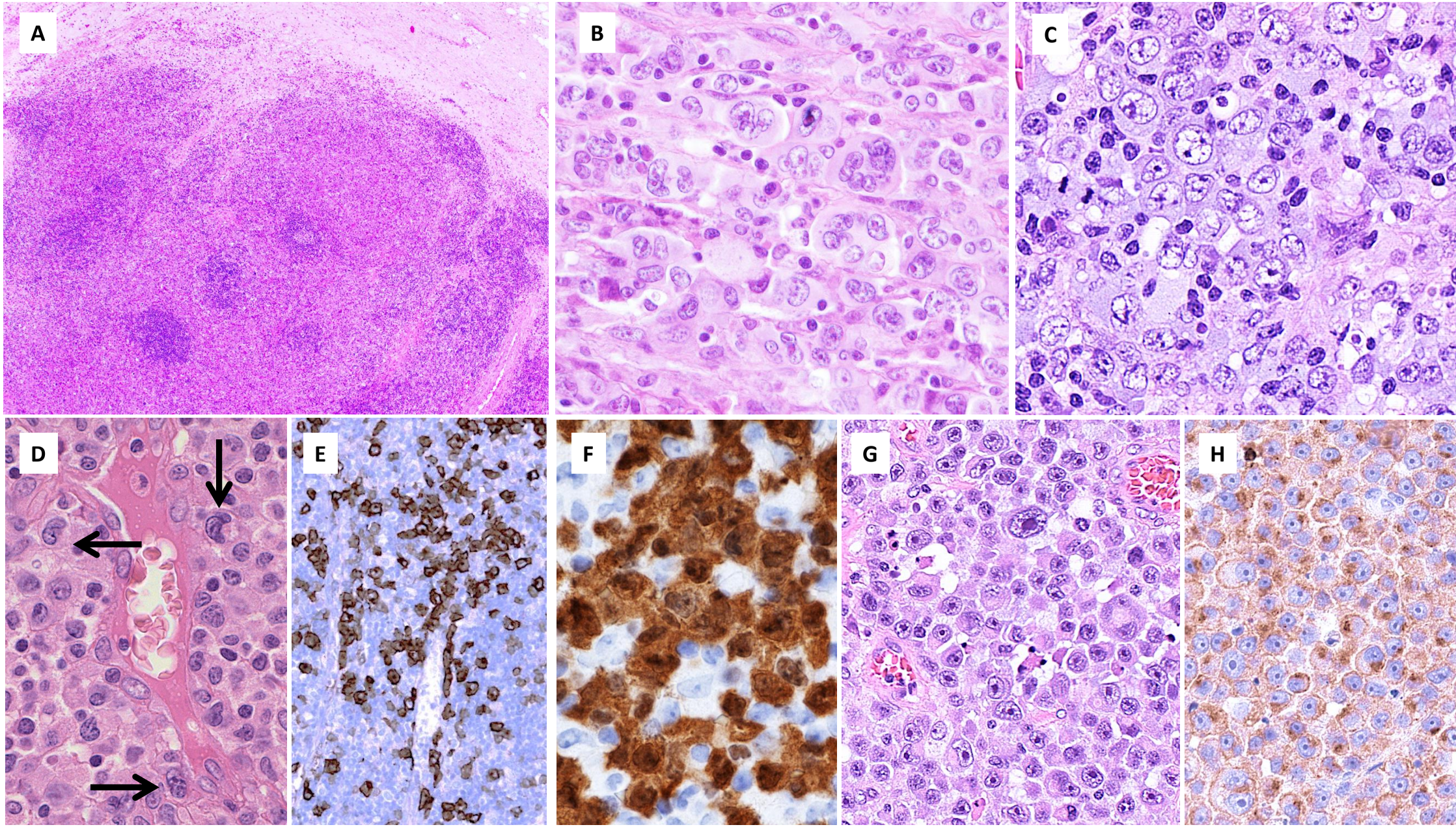
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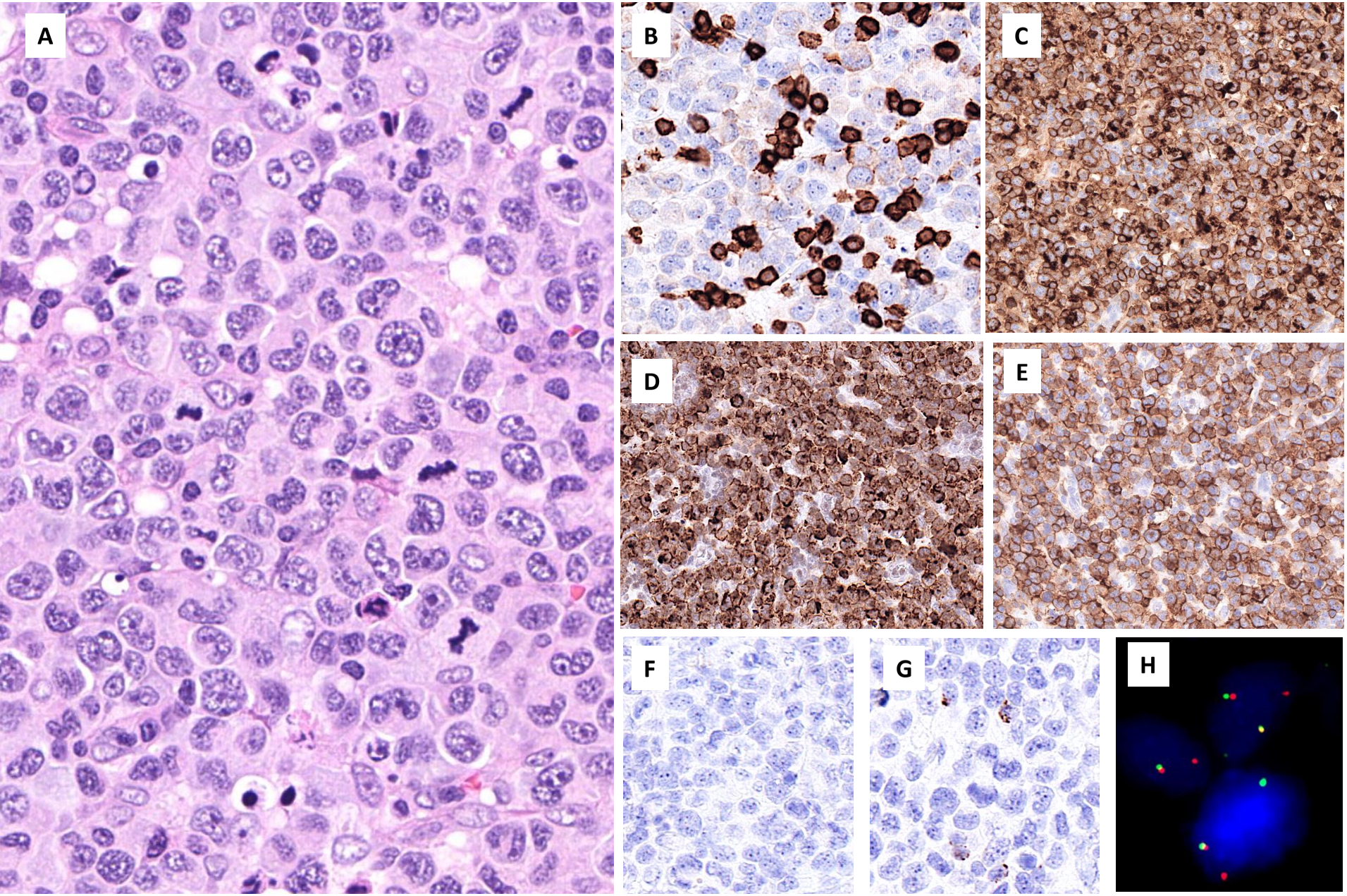
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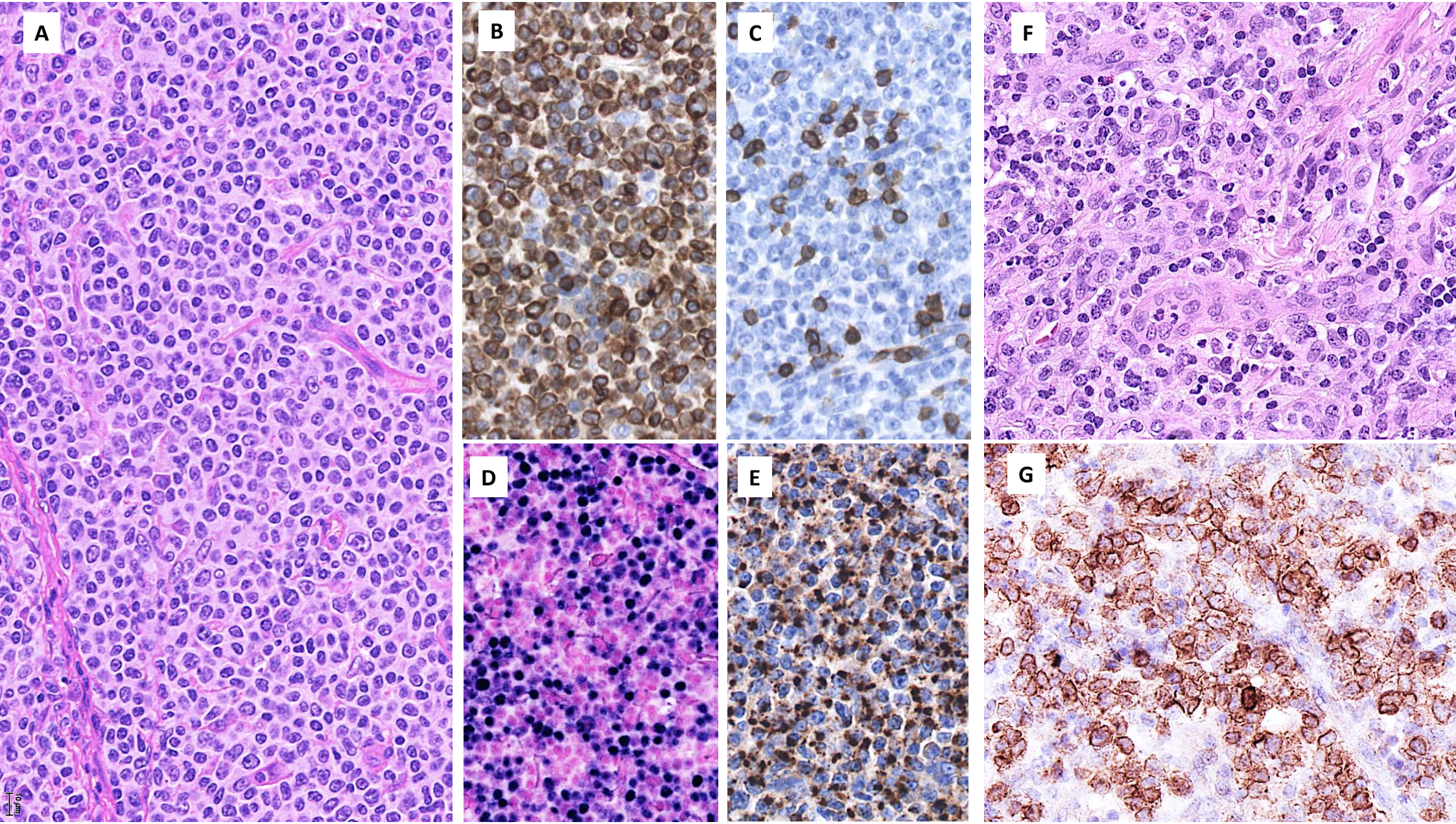
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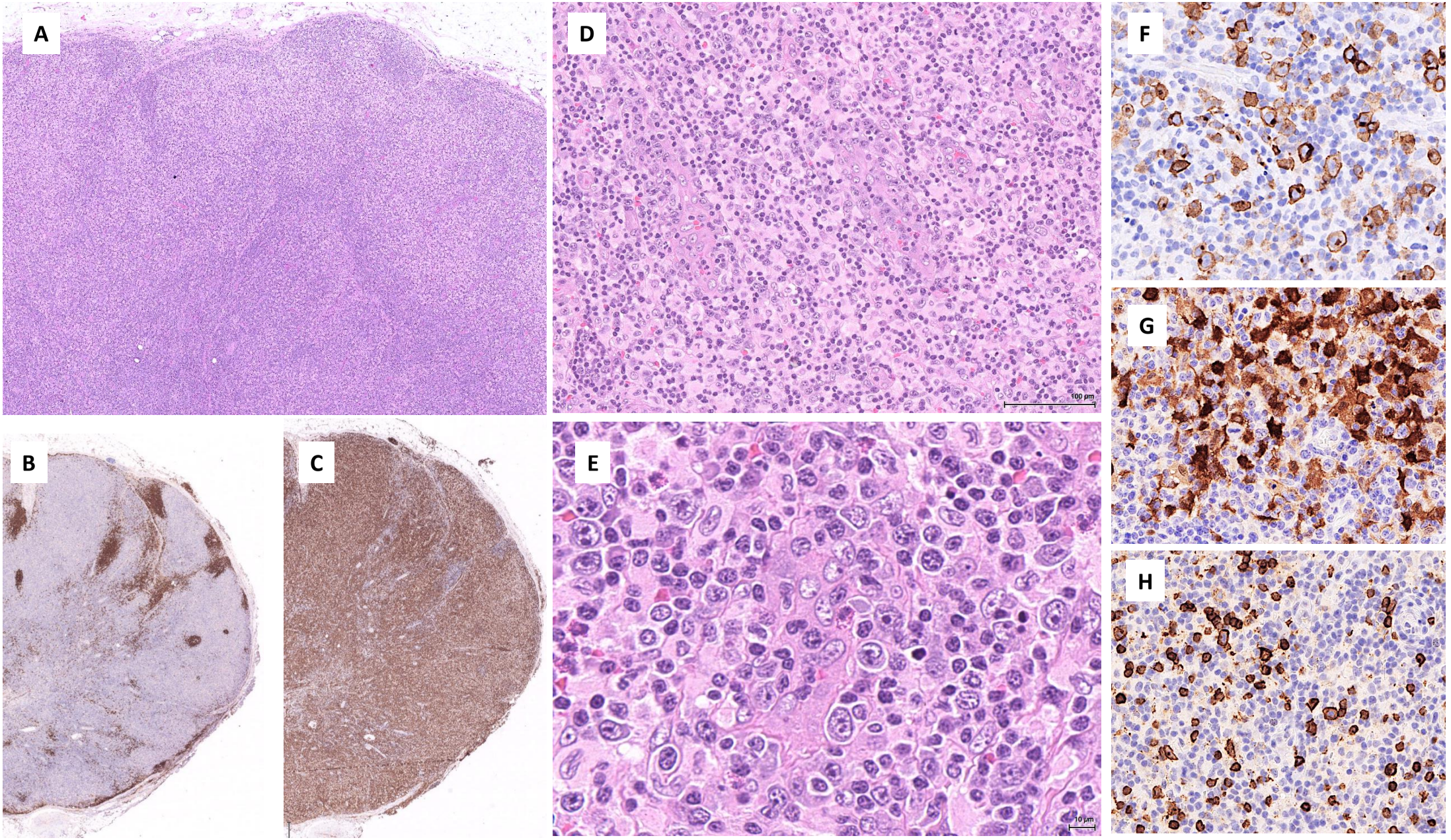
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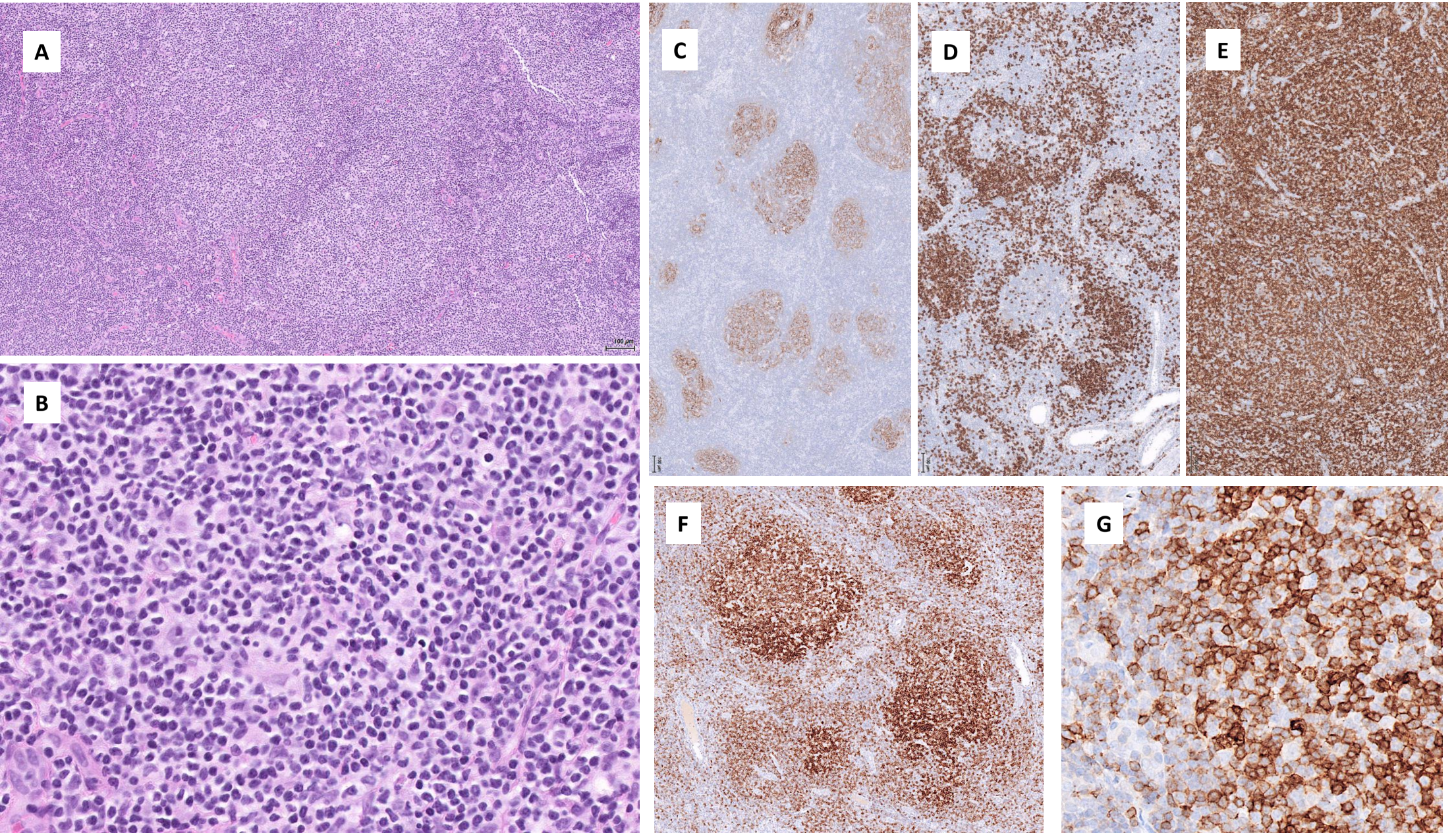
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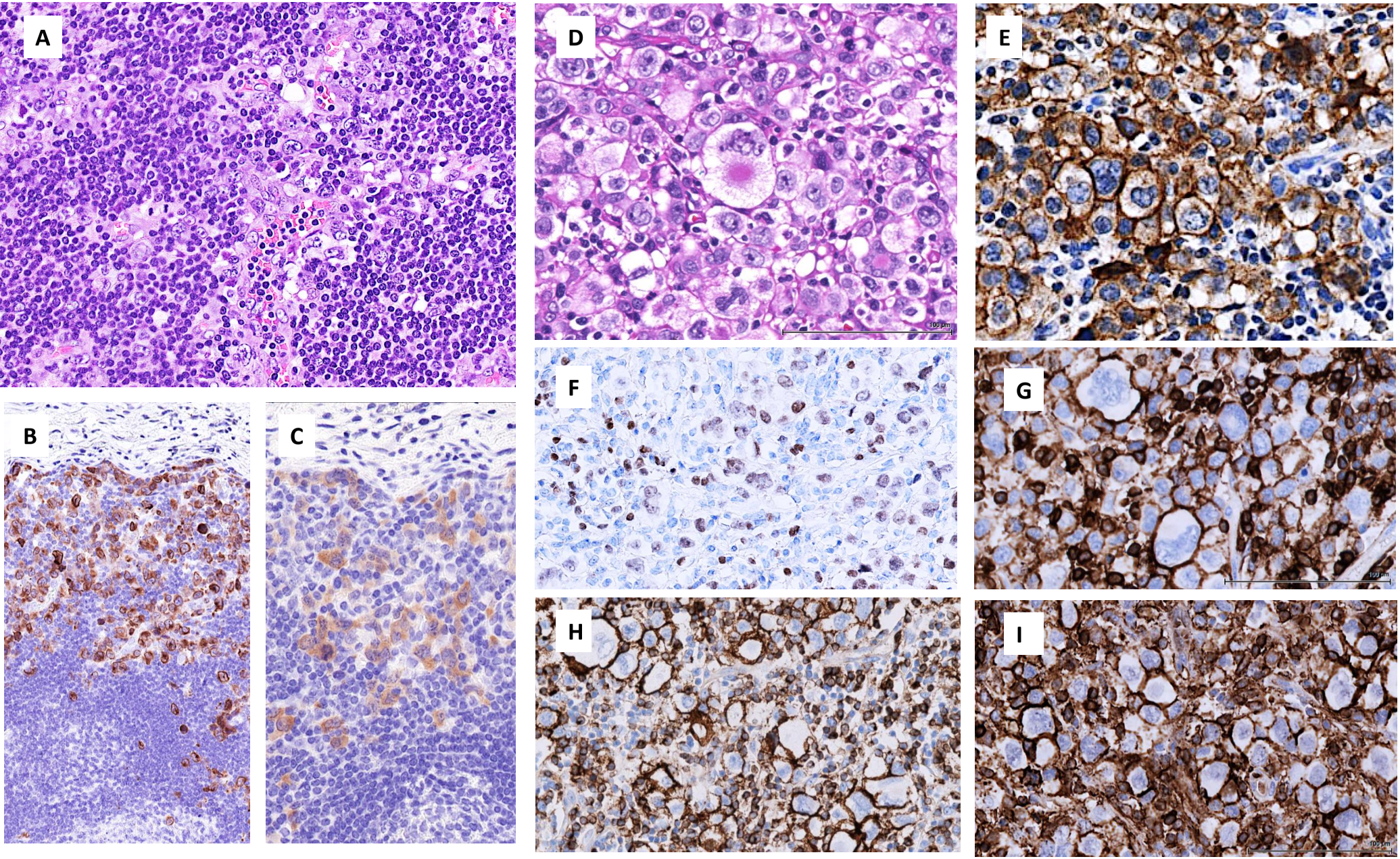
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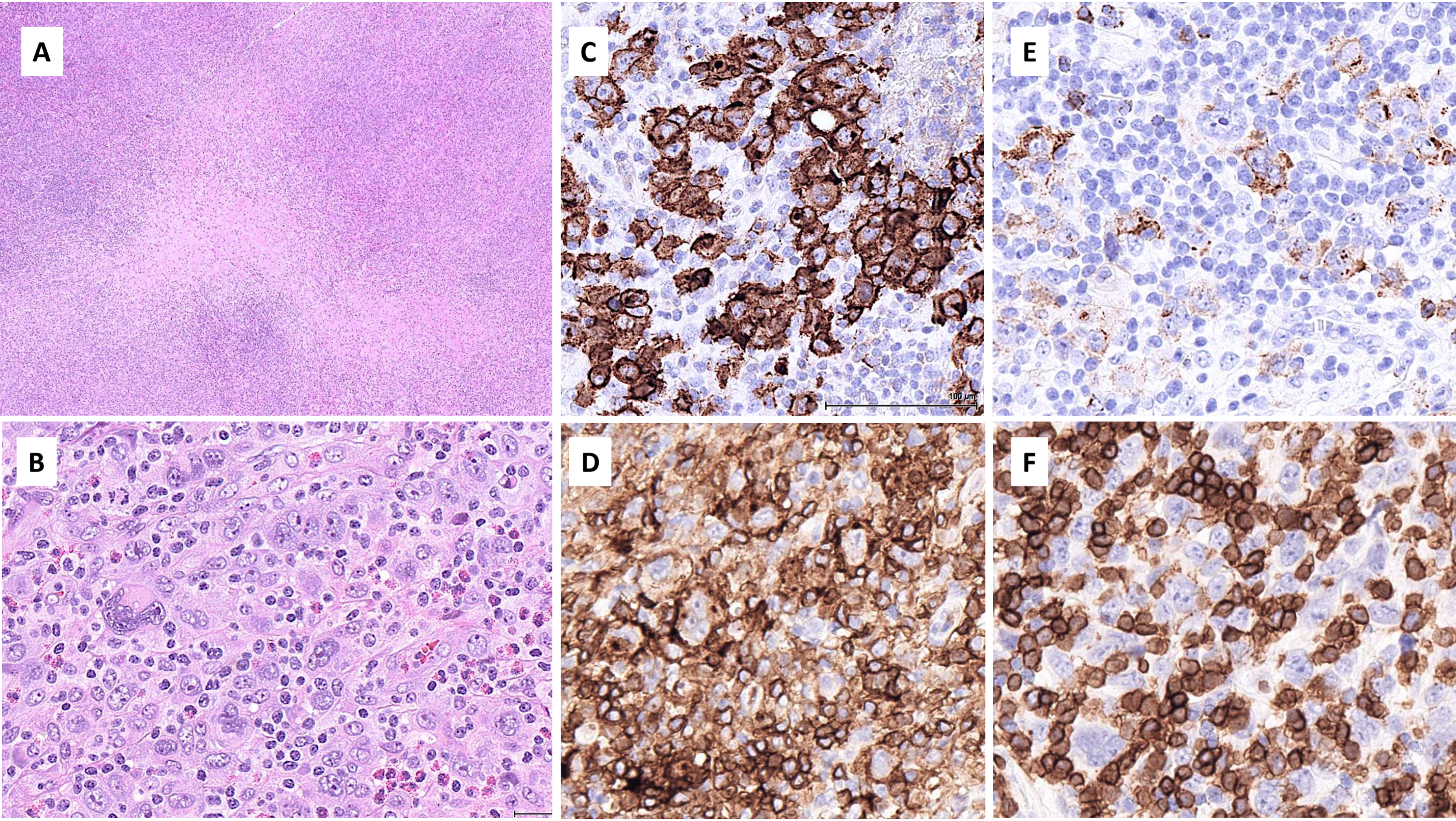
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