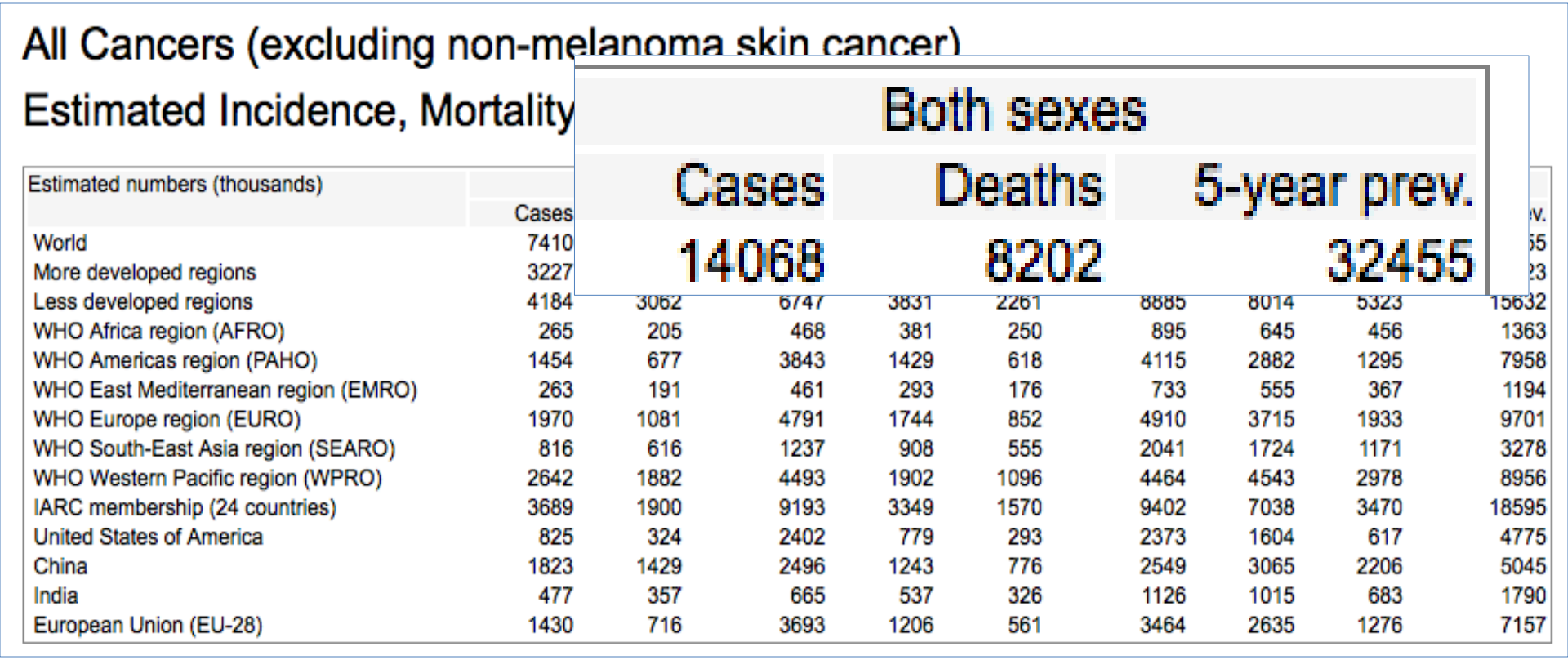
Lymphoma in immunosuppresed patients

Valdecilla
Instituto de Investigación Sanitaria
IDIVAL

Diagnosis of cancer: Room for improvement



All Cancers (excluding non-melanoma skin cancer)

Estimated Incidence, Mortality

Both sexes

Cases	Deaths	5-year prev.
14068	8202	32455

Estimated numbers (thousands)	Cases								
World	7410								65
More developed regions	3227								23
Less developed regions	4184	3062	6747	3831	2261	8885	8014	5323	15632
WHO Africa region (AFRO)	265	205	468	381	250	895	645	456	1363
WHO Americas region (PAHO)	1454	677	3843	1429	618	4115	2882	1295	7958
WHO East Mediterranean region (EMRO)	263	191	461	293	176	733	555	367	1194
WHO Europe region (EURO)	1970	1081	4791	1744	852	4910	3715	1933	9701
WHO South-East Asia region (SEARO)	816	616	1237	908	555	2041	1724	1171	3278
WHO Western Pacific region (WPRO)	2642	1882	4493	1902	1096	4464	4543	2978	8956
IARC membership (24 countries)	3689	1900	9193	3349	1570	9402	7038	3470	18595
United States of America	825	324	2402	779	293	2373	1604	617	4775
China	1823	1429	2496	1243	776	2549	3065	2206	5045
India	477	357	665	537	326	1126	1015	683	1790
European Union (EU-28)	1430	716	3693	1206	561	3464	2635	1276	7157

Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. In: IARC, Lyon; 2010. Prepared by Cancer research UK

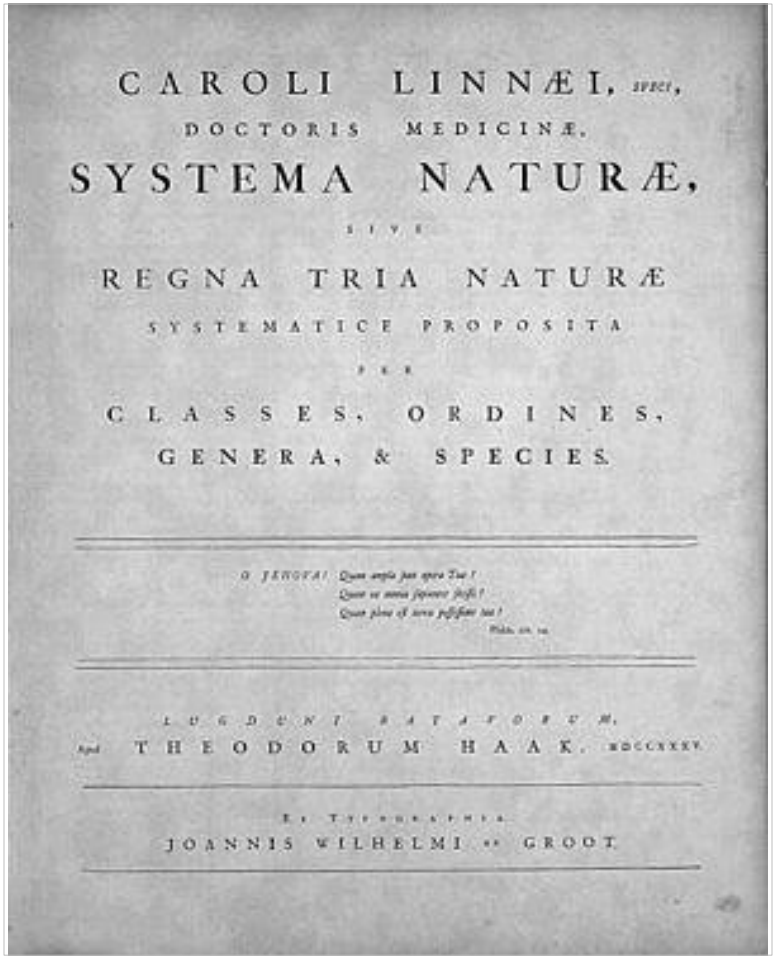
International Agency for Research on Cancer
World Health Organization

Hodgkin lymphoma, Leukaemia, Non-Hodgkin lymphoma, Multiple myeloma: both s
Estimated 1-year prevalent cancer cases (x1000), adult population

Lymphoma incidence across the world shows dramatic differences associated with:

- Ethnicity
- Environmental factors
- Specific infectious agents

Linnaeous
Rank-based method of classifying living organisms



CAROLI LINNÆI, *svec.*,

DOCTORIS MEDICINÆ,

SYSTEMA NATURÆ,

SIVE

REGNA TRIA NATURÆ

SYSTEMATICE PROPOSITA

PER

CLASSES, ORDINES,

GENERA, & SPECIES.

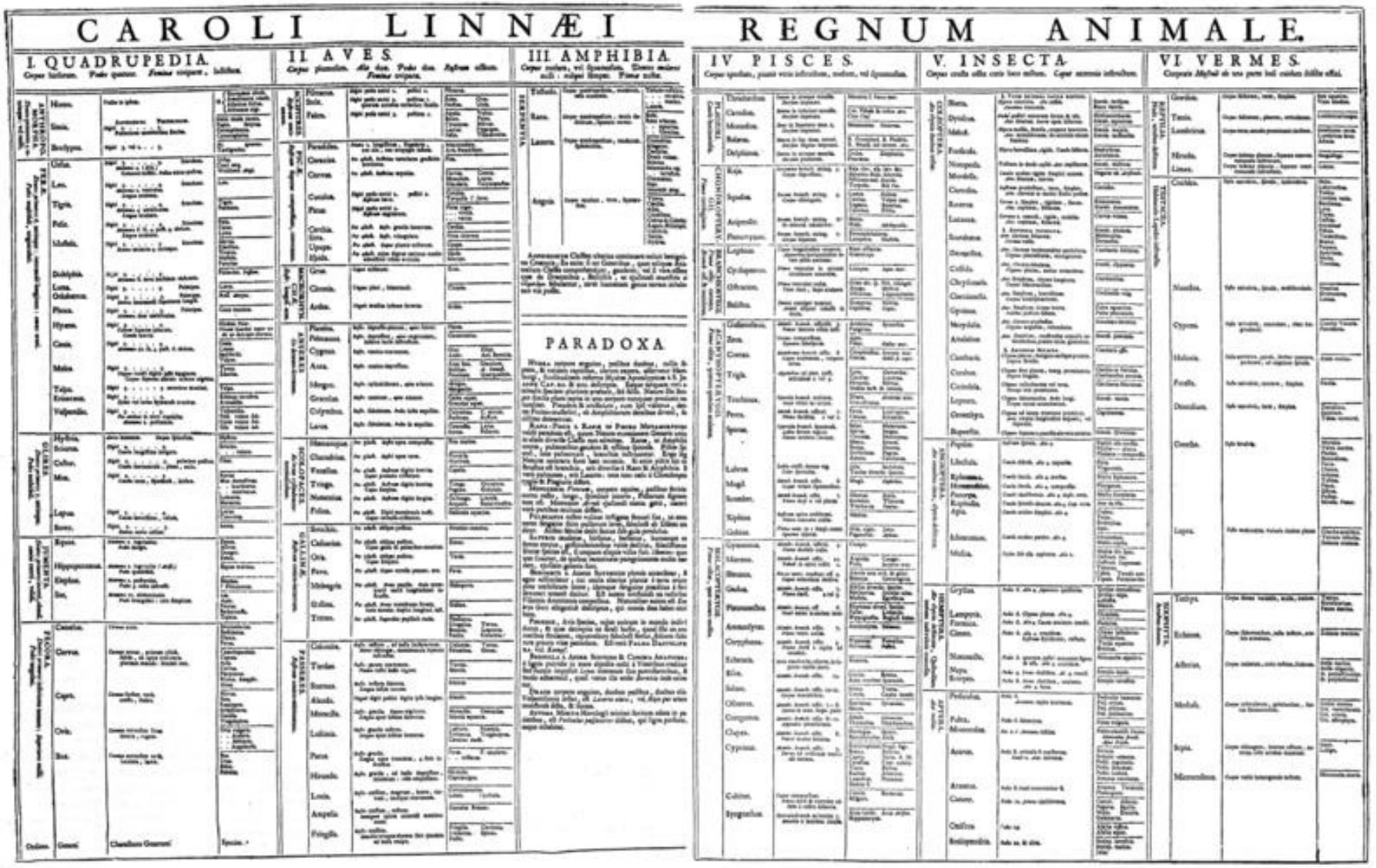
O JEHOVA! Quam ampla sunt opera Tua!
Quam ea omnia sapienter fecisti!
Quam plena est terra possessione tua!
Psalm. civ. 24.

LUGDUNI BATAVORUM,

Apud THEODORUM HAAK, MDCCXXXV.

Ex Typographia

JOANNIS WILHELMI *de* GROOT.

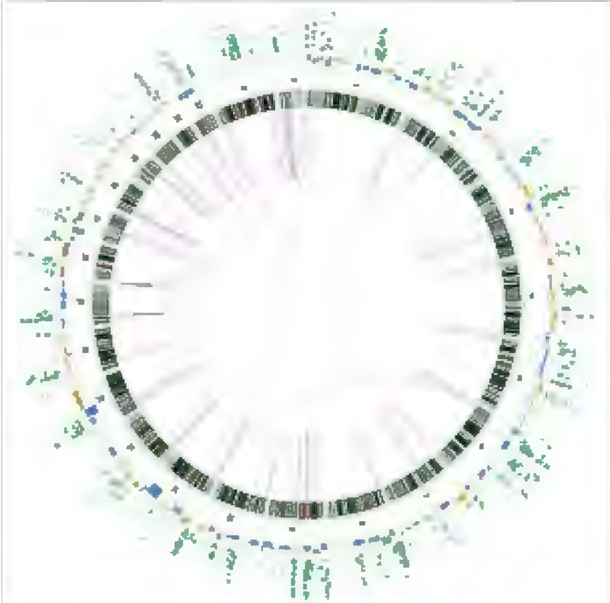

CAROLI LINNÆI
REGNUM ANIMALE.
I. QUADRUPEDIA.
II. AVES.
III. AMPHIBIA.
IV. PISCES.
V. INSECTA.
VI. VERMES.
PARADOXA

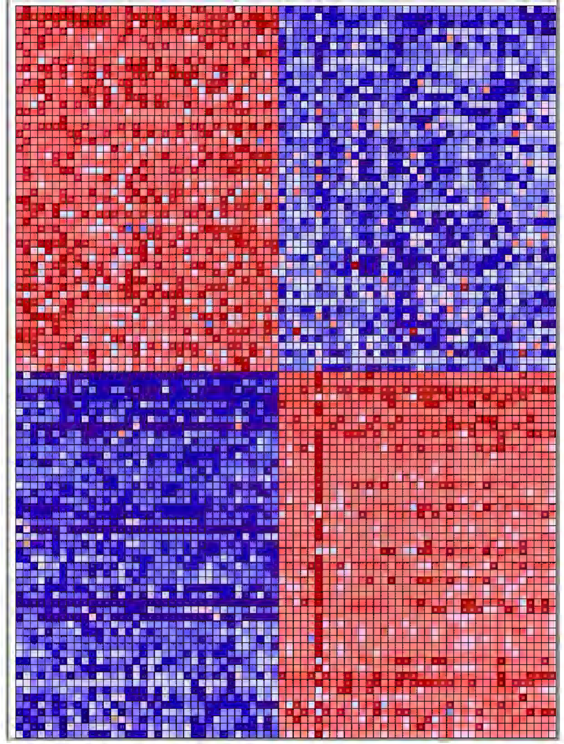
The role of the pathologists in cancer classification

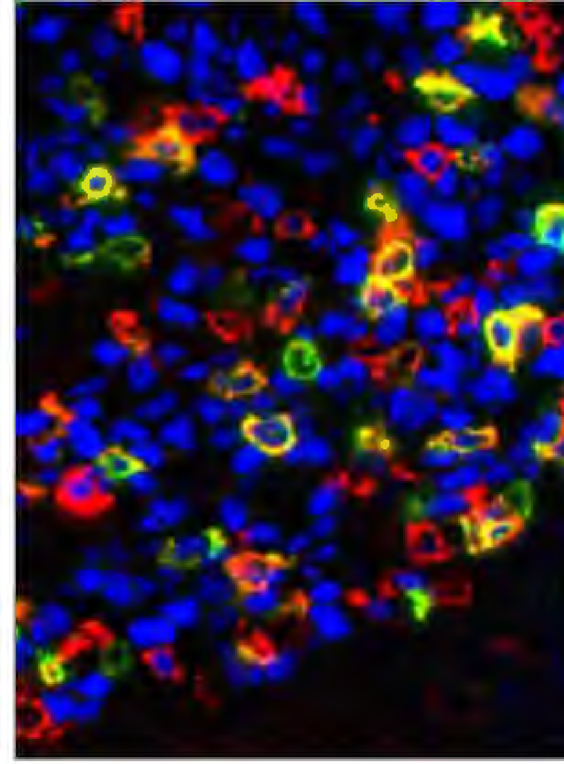
Taxonomy is the systems that allows to assign treatment based on the morphology/ immunophenotype/molecular features of the disease

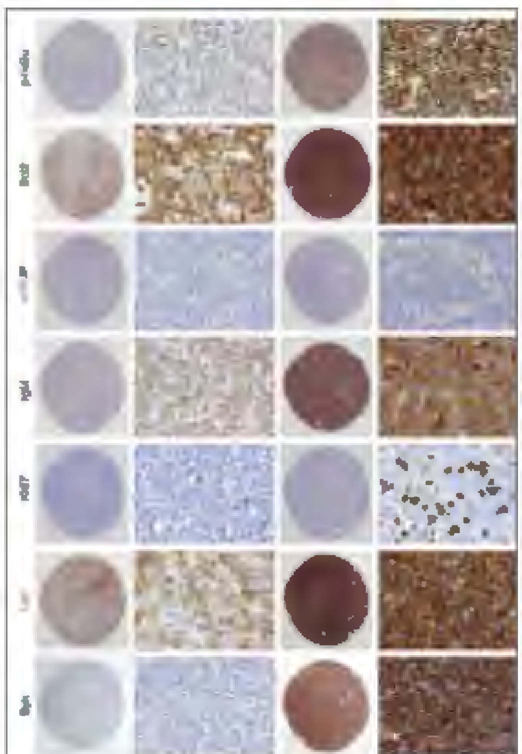
Precise c s leads to the id

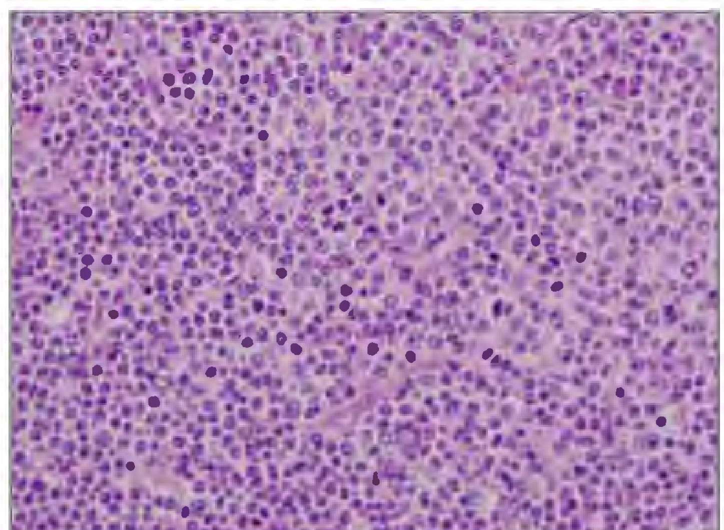
- und
- targ
- predictive and prognostic markers for patient











WHO Classification of T/NK-cell Neoplasms

- **T-cell prolymphocytic leukemia**
- **T-cell large granular lymphocytic leukemia**
- **Chronic lymphoproliferative disorder of NK cells**
- **Aggressive NK cell leukemia**
- **Systemic EBV+ T-cell Lymphoma of childhood***
- **Hydroa vacciniforme-like lymphoproliferative disorder***
- **Adult T-cell leukemia/lymphoma**
- **Extranodal NK/T-cell lymphoma, nasal type**
- **Enteropathy-associated T-cell lymphoma**
- **Monomorphic epitheliotropic intestinal T-cell lymphoma***
- **Indolent T-cell lymphoproliferative disorder of the GI tract ***
- **Hepatosplenic T-cell lymphoma**
- **Subcutaneous panniculitis- like T-cell lymphoma**
- **Mycosis fungoides**
- **Sezary syndrome**
- **Primary cutaneous CD30 positive T-cell lymphoproliferative disorders**
- **Lymphomatoid papulosis**
- **Primary cutaneous anaplastic large cell lymphoma**

WHO Classification of B-cell Neoplasms

- **Chronic lymphocytic leukemia /small lymphocytic lymphoma**
- **Monoclonal B-cell lymphocytosis***
- **B-cell prolymphocytic leukemia**
- **Splenic marginal zone lymphoma**
- **Hairy cell leukemia**
- **Splenic B-cell lymphoma/leukemia, unclassifiable**
- **Splenic diffuse red pulp small B-cell lymphoma**
- **Hairy cell leukemia-variant**

WHO Classification of B-cell Neoplasms

Precursor B-lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

- B-cell CLL/SLL
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma
- **Plasma cell myeloma/plasmacytoma**
- Extranodal marginal zone B-cell lymphoma (MALT type)
- Primary mediastinal large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Nodal marginal zone B-cell lymphoma

WHO Classification of Hodgkin Lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma

Classical Hodgkin lymphoma

- Nodular sclerosis CHL
- Lymphocyte-rich CHL
- Mixed cellularity CHL
- Lymphocyte depleted CHL

Classification of Post-transplant Lymphoproliferative Disorders (PTLDs)

Non-destructive PTLD: Plasmacytic hyperplasiaInfectious mononucleosisFlorid follicular hyperplasia

Polymorphic PTLD

Monomorphic PTLD (Classify according to the lymphoma they resemble)

B-cell neoplasms Diffuse large B-cell lymphoma, not otherwise specifiedBurkitt's lymphoma Plasma cell myelomaPlasmacytomaOther*

T-cell neoplasms Peripheral T-cell lymphoma, not otherwise specified

Hepatosplenic T-cell lymphoma

Other

Classical Hodgkin's Lymphoma PTLD From Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC Press; 2017.*

PTLD Frequency

PTLDs develop in approximately 2% of all transplant recipients, but there is a significant variation in incidence based on the type of organ transplanted:

- kidney, 0.5% to 2.5%;
- marrow or stem cell, 1% to 2%;
- liver, 1% to 10%;
- heart and lung, 2% to 10%; and
- intestinal and multivisceral, 5% to 20%

Neuringer: Posttransplant lymphoproliferative disease after lung transplantation. *Clin Dev Immunol. 2013:430209 2013 10*
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D Dierickx, T Tousseyn, X Sagaert, et al.: Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. Leuk Lymphoma. 54:2433-2440 2013

PTLD; factors implied in the incidence

EBV seronegativity (transplanting an organ from an EBV-seropositive donor into an EBV-seronegative recipient (EBV mismatch) increases the incidence of PTLD 10- to 75-fold)

CMV mistmatch

HCV-induced cirrhosis

Young age (early PTLD)

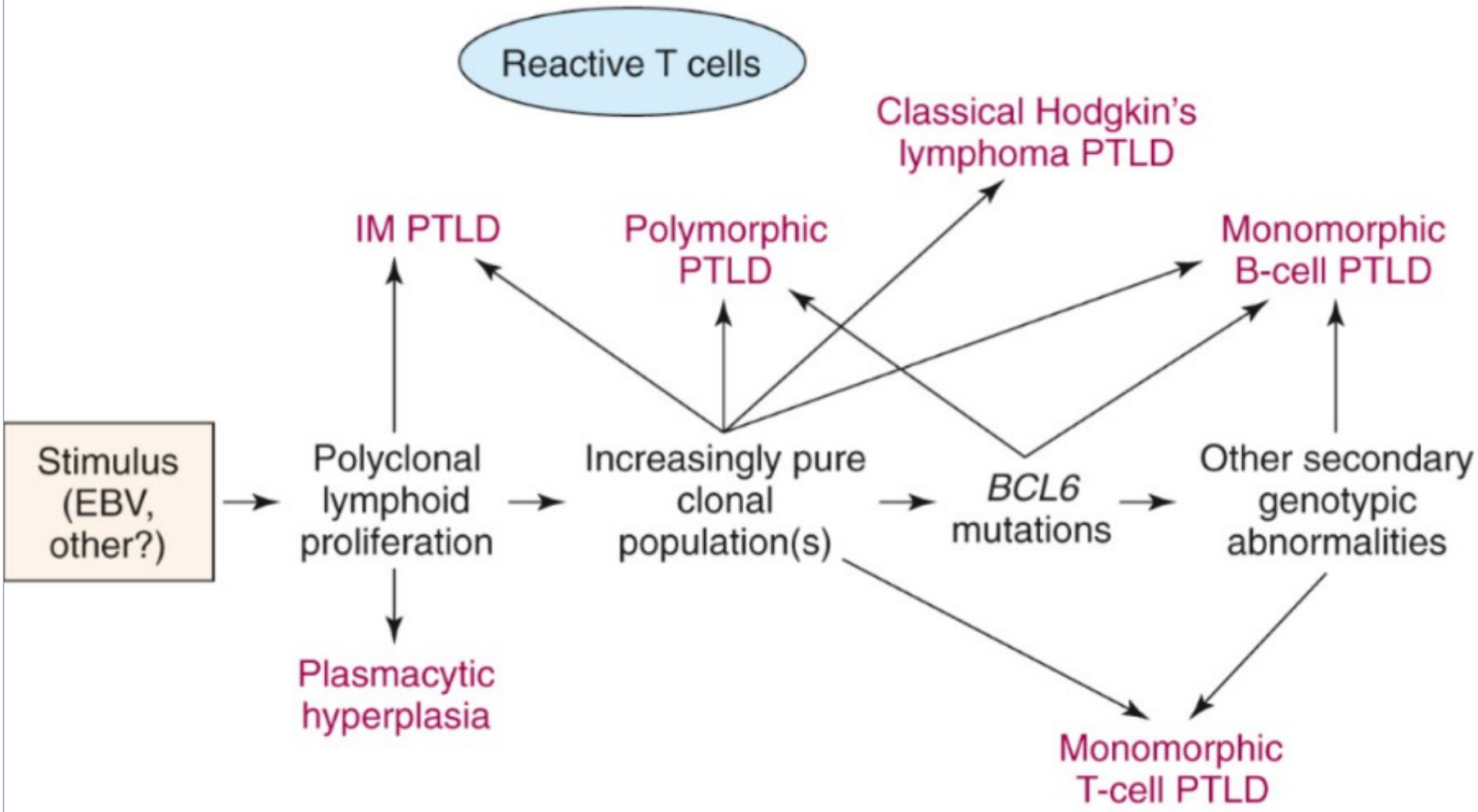
Advanced age (late PTLD)

Genetic background (cytokine polymorphisms)

Immunosuppressive regimen

PTLD; etiology

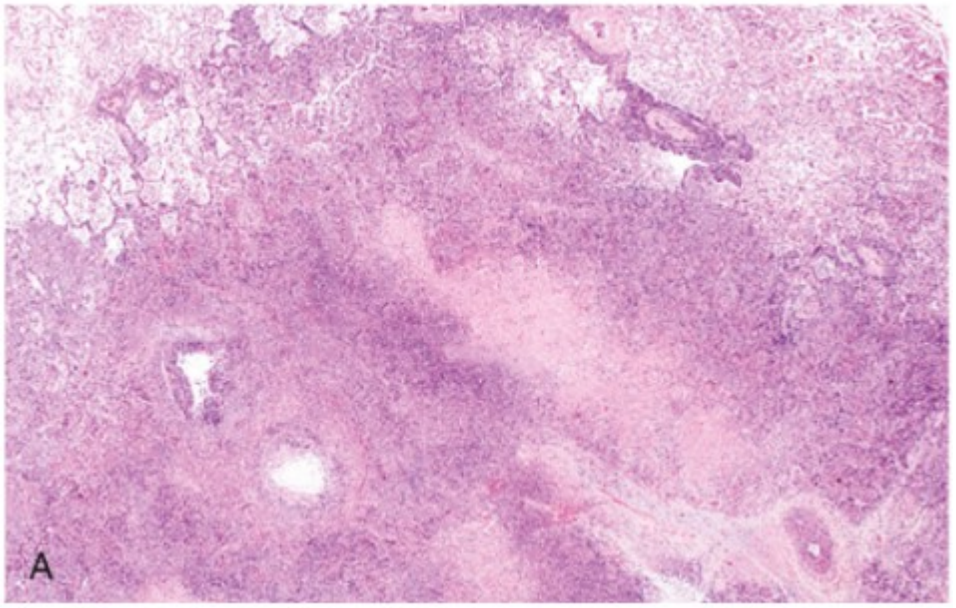
- Most PTLDs after solid organ transplantation are derived from recipient lymphoid cells
- PTLDs occurring after bone marrow transplantation are most often donor derived
- PTLDs limited to the allograft after solid organ transplantation are more frequent from the donor origin
- The majority of PTLDs are caused by EBV-infected lymphoid or plasmacytic cells that are not adequately controlled by the immune system because of immunosuppression or myeloablative regimens
- EBV may be acquired from the donor, primary infection, superinfection or reactivation

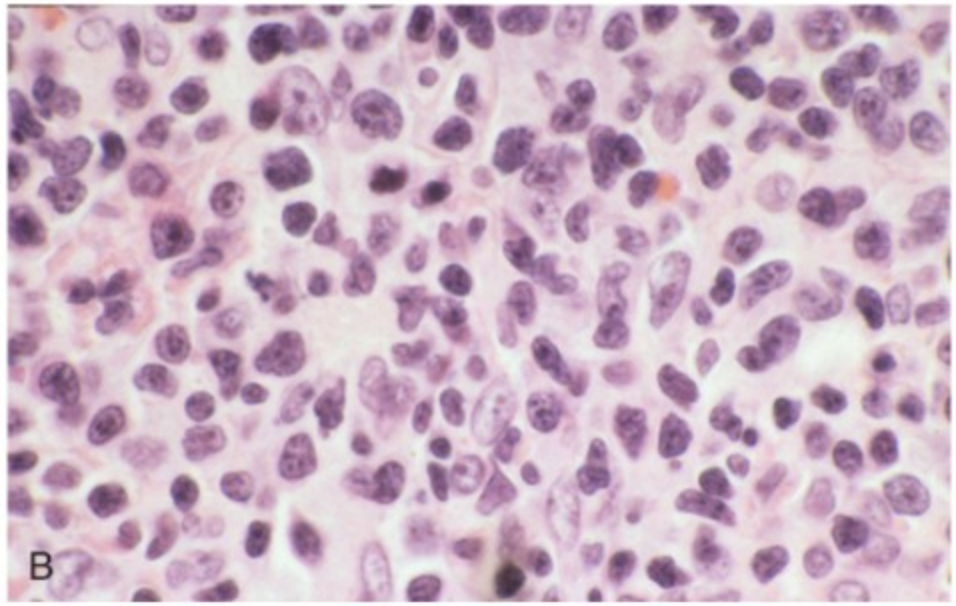


S Sdwerdlow, F Craig, Hematopathology, 2016

Polymorphic Post-transplant Lymphoproliferative Disorder

- Diffuse and destructive proliferation of variably sized lymphocytes, plasma cells, transformed cells, and immunoblasts
- Hodgkin-like features
- Geographic areas of necrosis, often associated with neutrophils and histiocytes, and surrounded by increased numbers of transformed cells or immunoblasts
- Some PTLDs fulfill the criteria for EBV+ mucocutaneous ulcer (MCU)
- T-cell lymphomas are more frequently polymorphous, listed apart





Lymphoproliferative disorder pathogenesis

- Recruitment of lymphoid tissue
  - Gastritis by helicobacter pylori
- Lymphoproliferative disorder (polymorphous/monomorphous)
  - Induced by lymphotropic virus (EBV, HCV, HTLV,…)
    - Infectious mononucleosis
  - Autoimmune disorder, self-antigen recognition
    - Still disease
  - Multifactorial: Kikuchi disease

- AM Evens, R Roy, D Sterrenberg, et al.: Post-transplantation lymphoproliferative disorders: diagnosis, prognosis, and current approaches to therapy. *Curr Oncol Rep. 12:383-394 2010 13*
- *J Morscio, D Dierickx, T Tousseyn: Molecular pathogenesis of B-cell posttransplant lymphoproliferative disorder: what do we know so far?. Clin Dev Immunol. 2013:150835 2013 16*
- *D Dierickx, T Tousseyn, X Sagaert, et al.: Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. Leuk Lymphoma. 54:2433-2440 2013 67*
- *Z Al-Mansour, BP Nelson, AM Evens: Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. Curr Hematol Malig Rep. 8:173-183 2013 74J Morscio, D Dierickx, JF Ferreiro, et al.: Gene expression profiling reveals clear differences between EBV-positive and EBV-negative posttransplant lymphoproliferative disorders. Am J Transplant. 13:1305-1316 2013 110*
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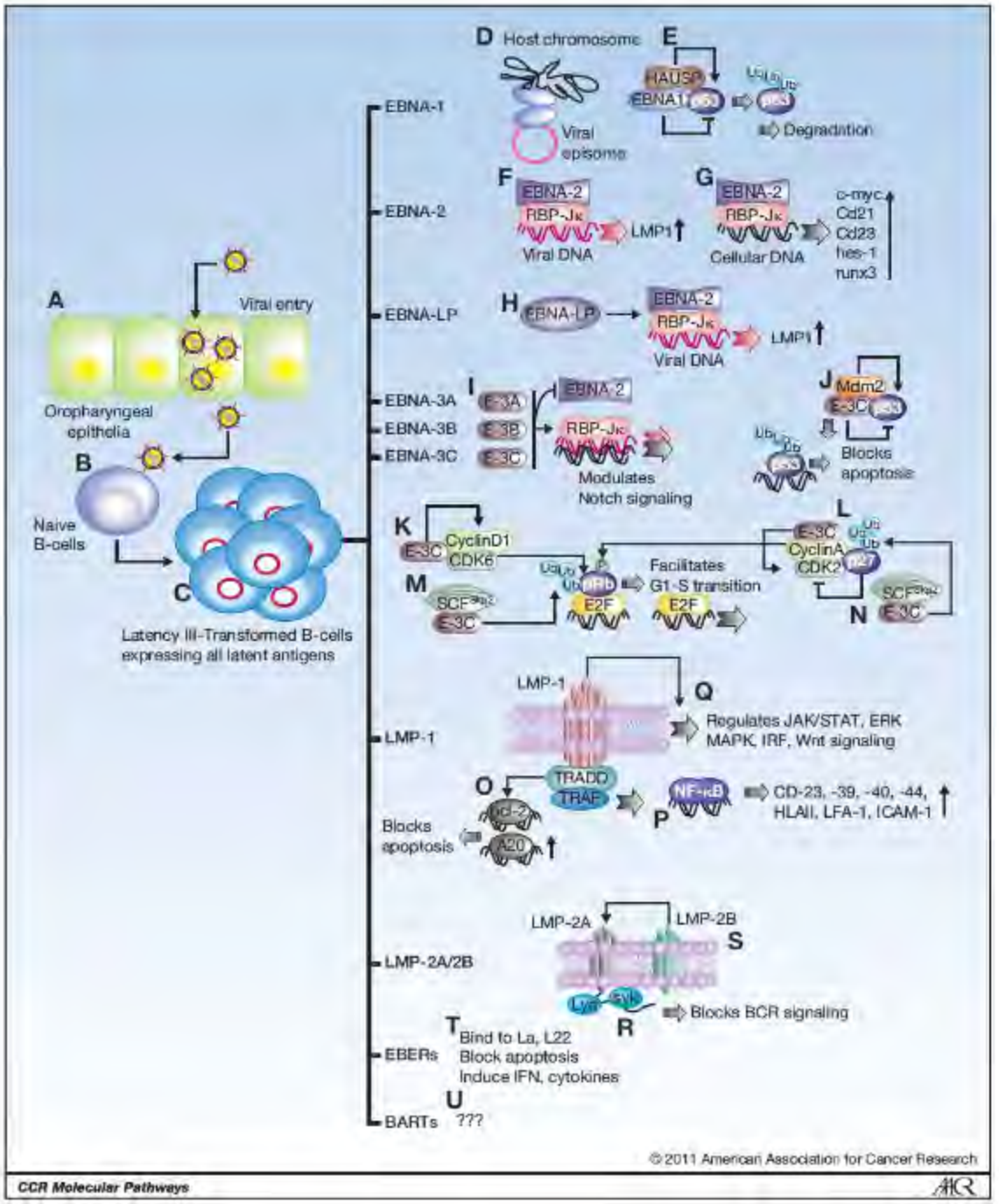
- *R Reshef, S Vardhanabhuti, MR Luskin, et al.: Reduction of immunosuppression as initial therapy for*

EBV infection
from Infectious Mononucleosis to aggressive lymphoma



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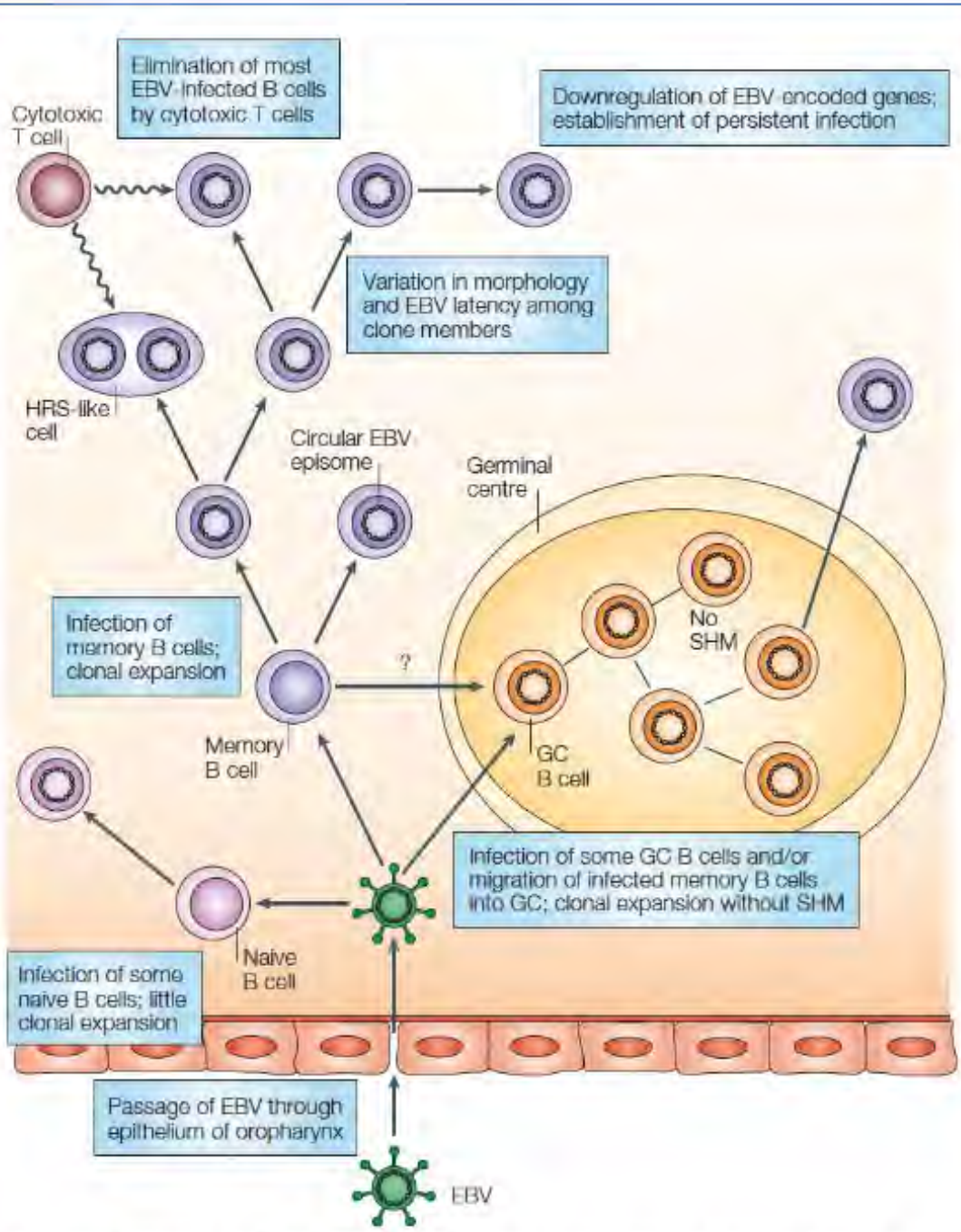
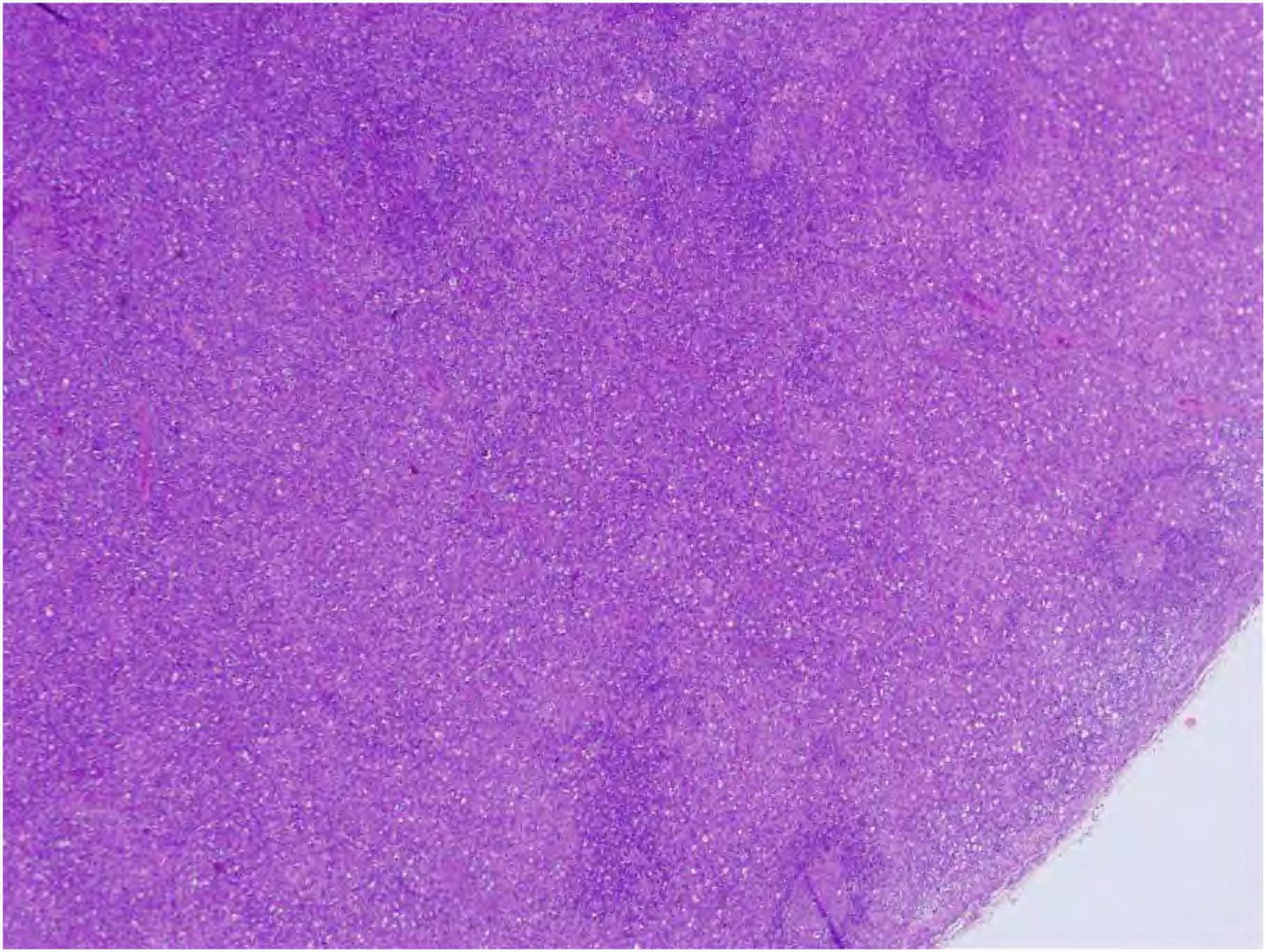
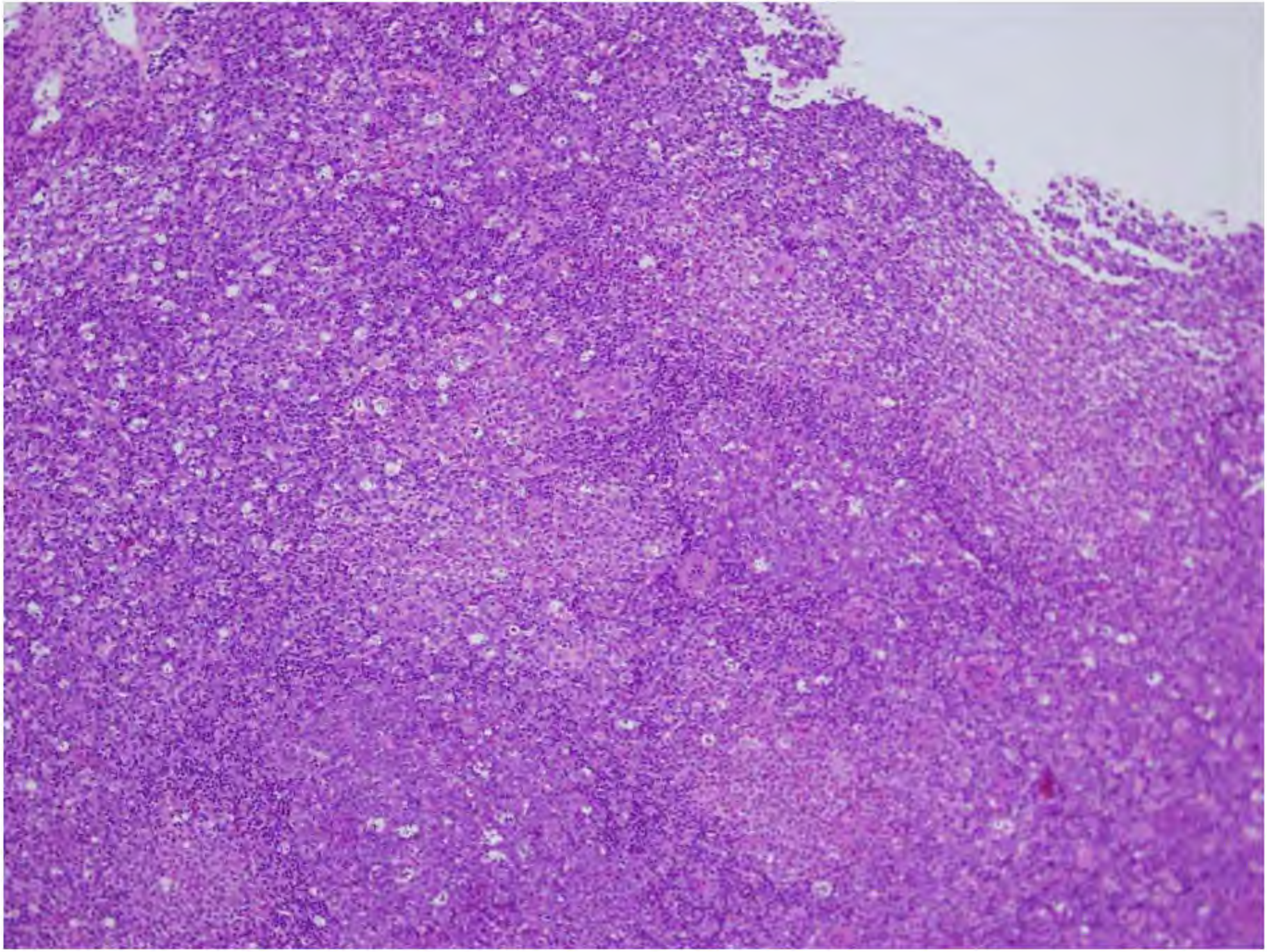
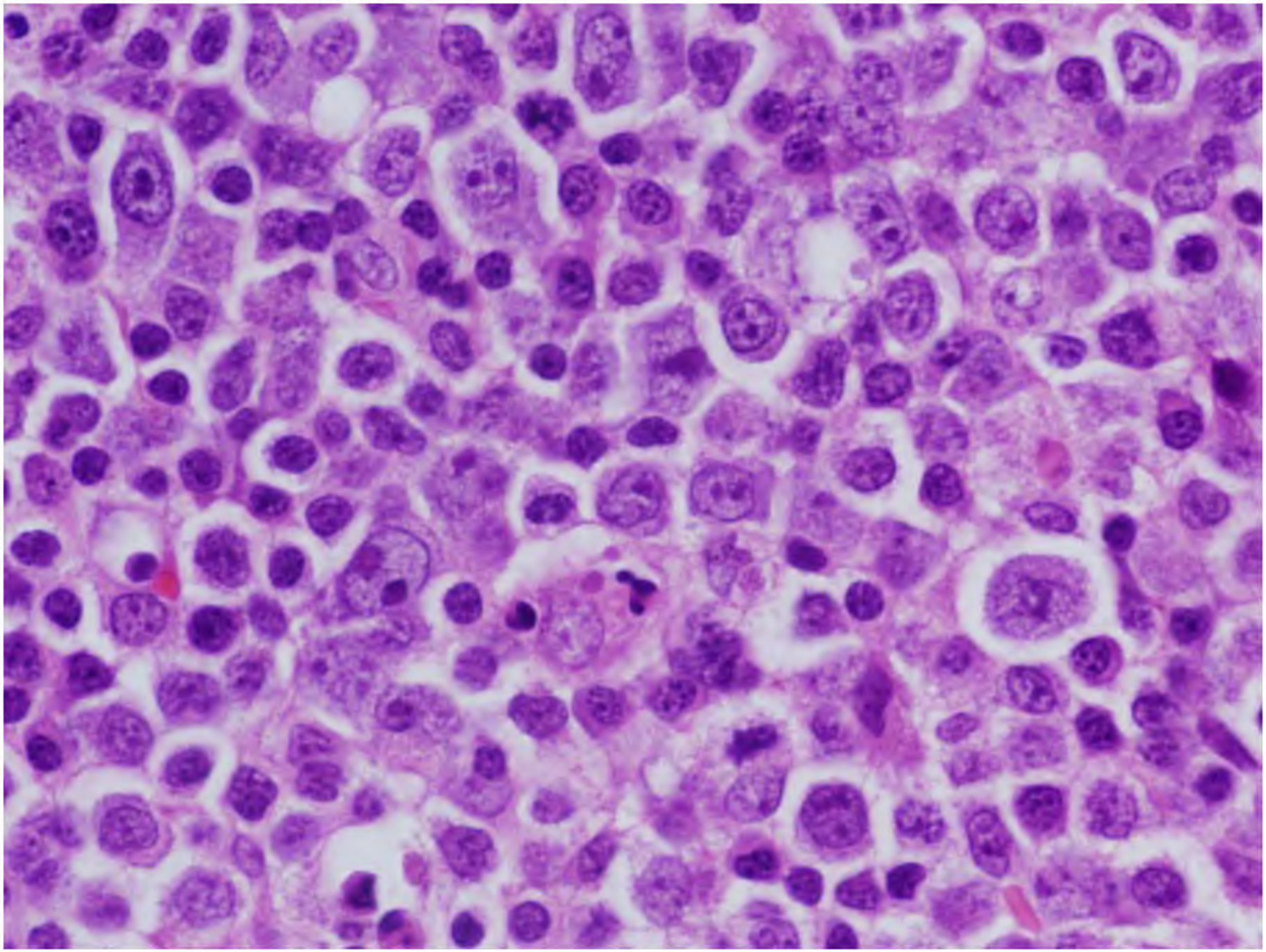


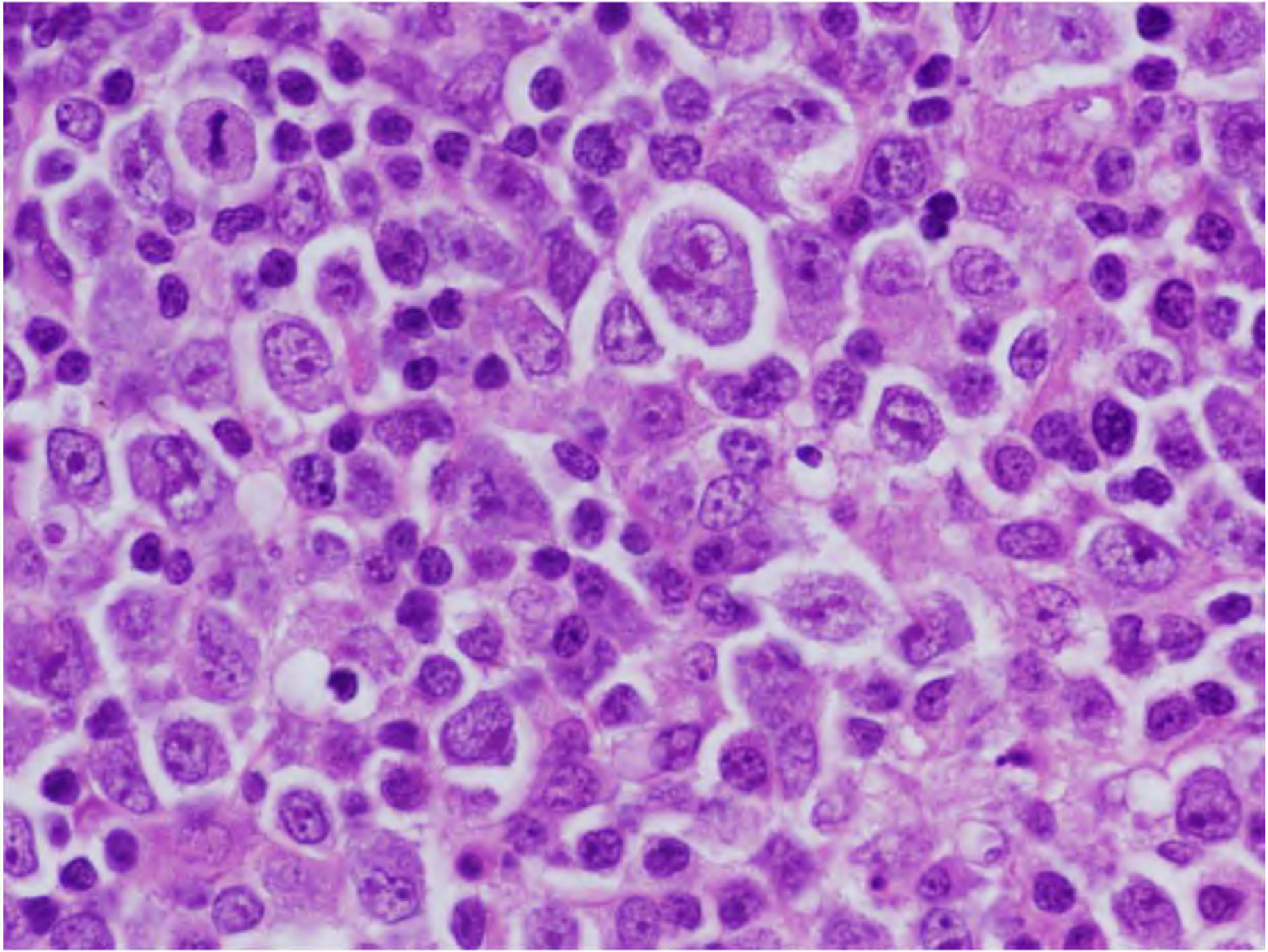
Figure 1 | **Strategies of EBV-infected B cells during acute primary infection.** Epstein–Barr

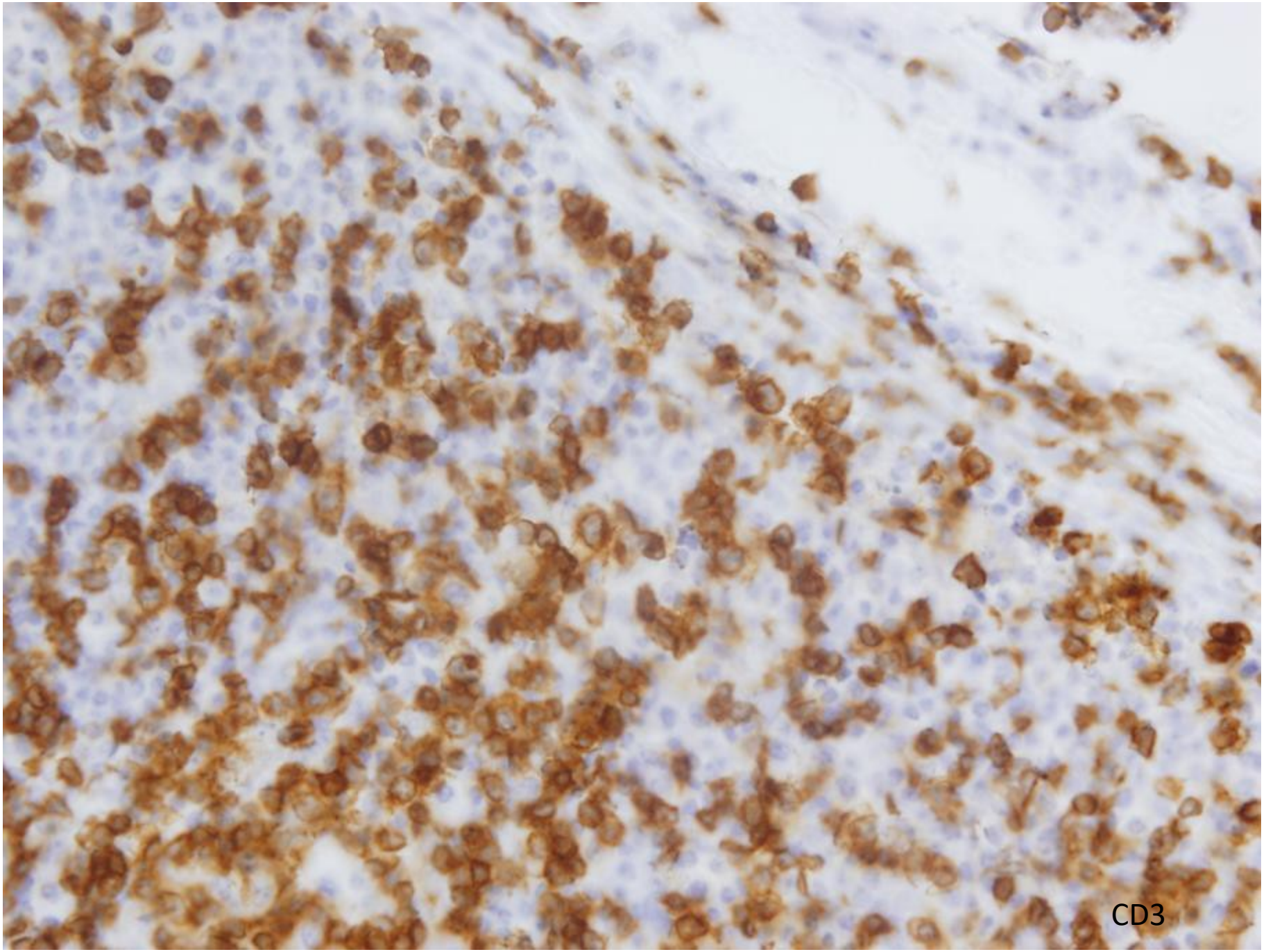
Case 1

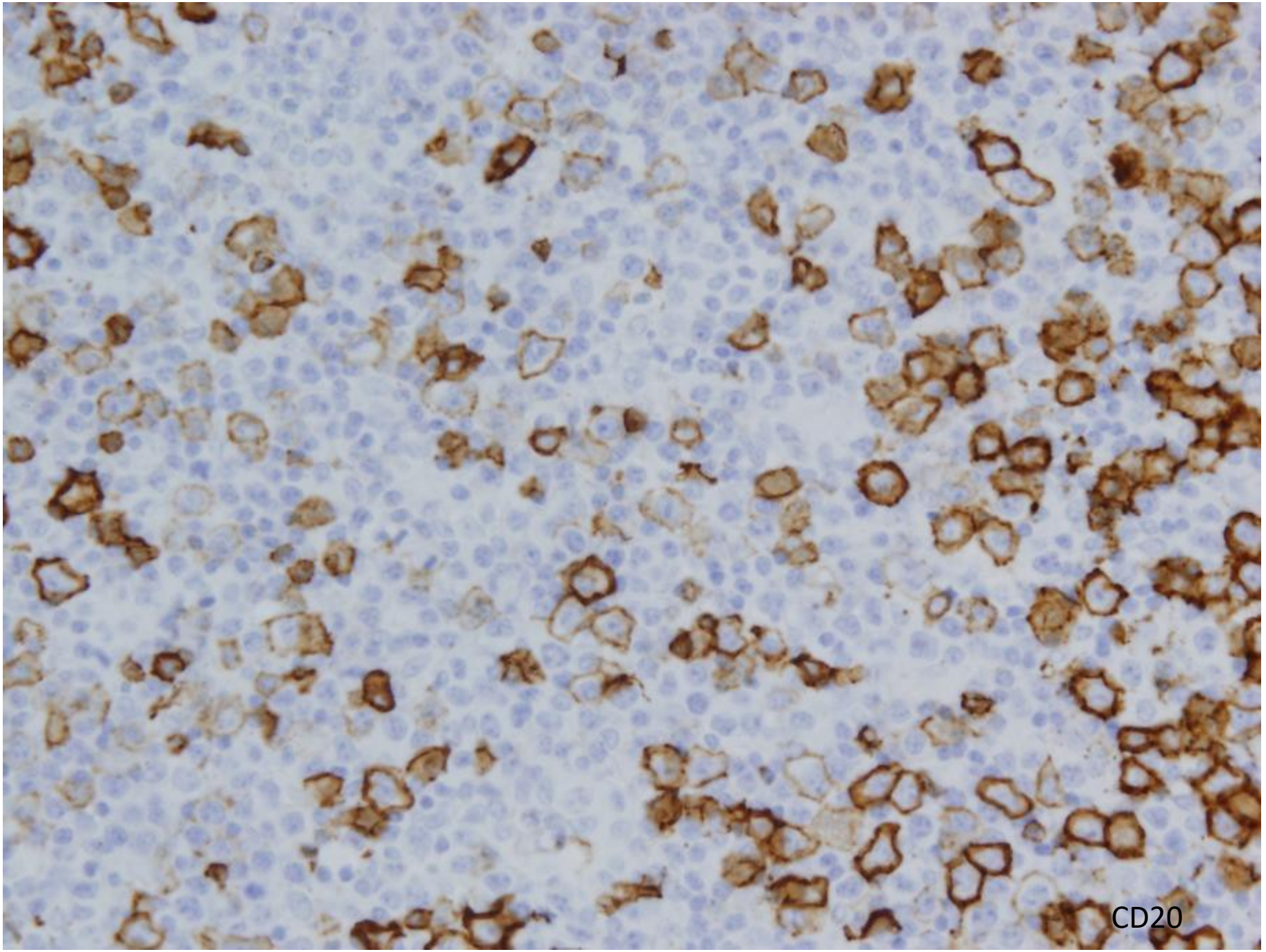









CD3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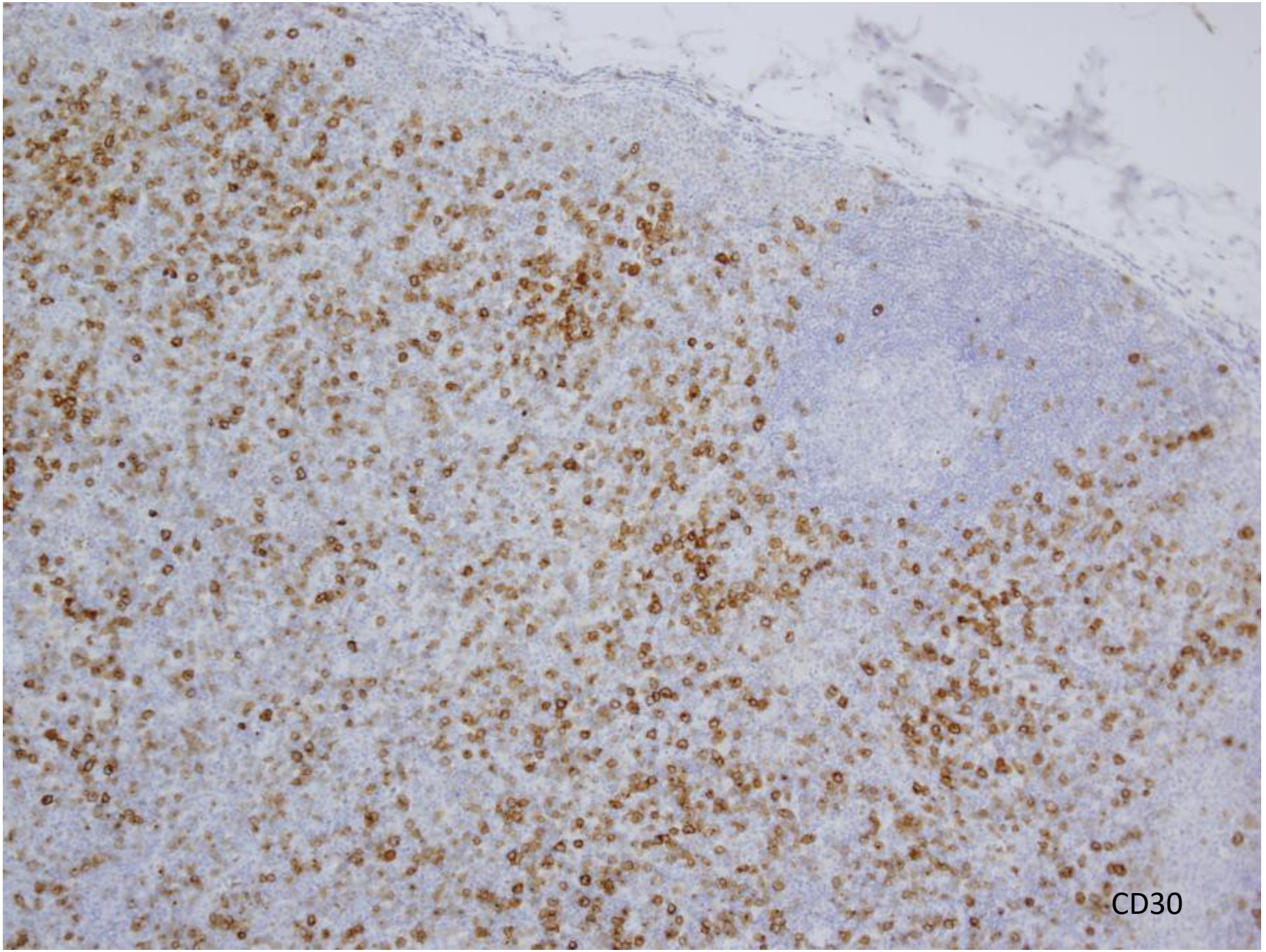
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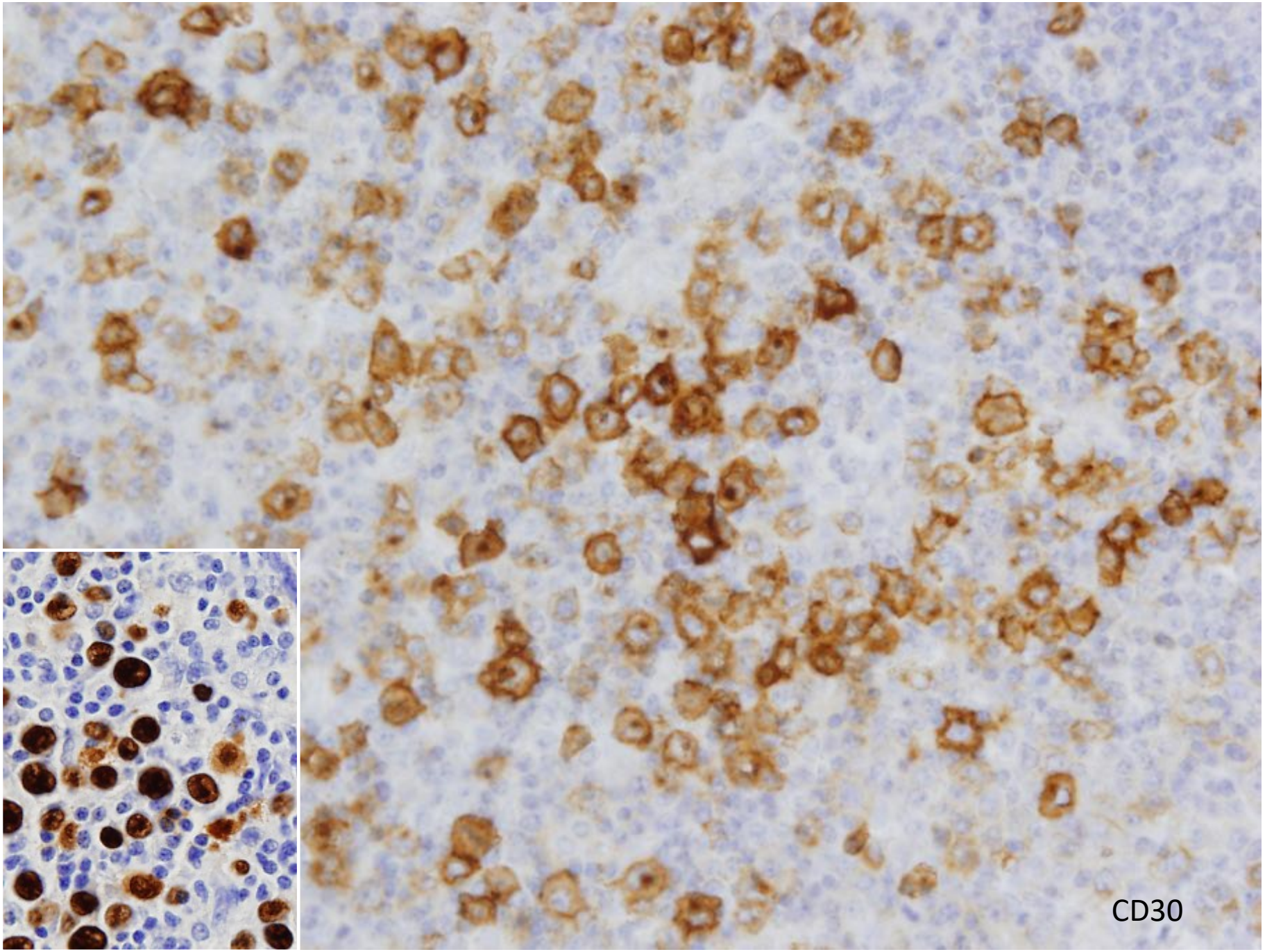
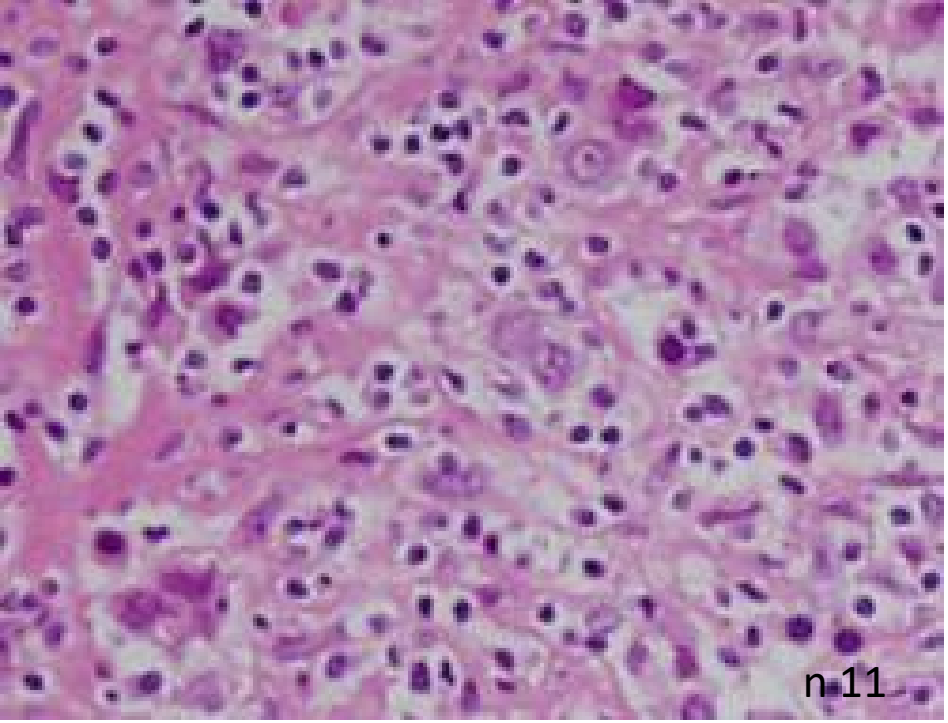

CD30

Infectious mononucleosis

Case 2

75 yrs old male
Disseminated lymphadenopathies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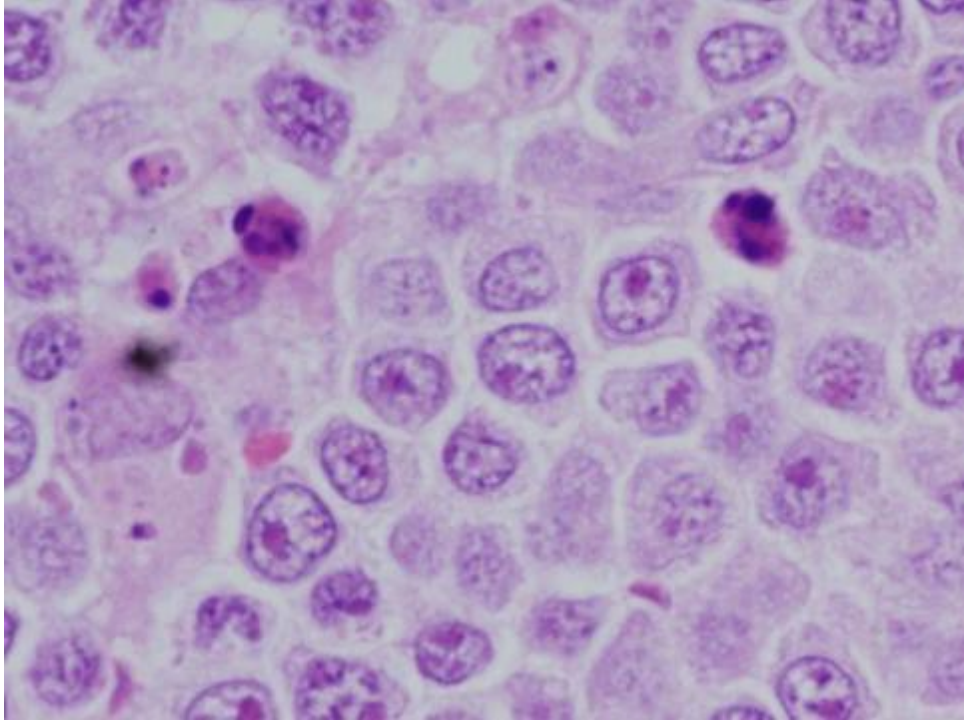
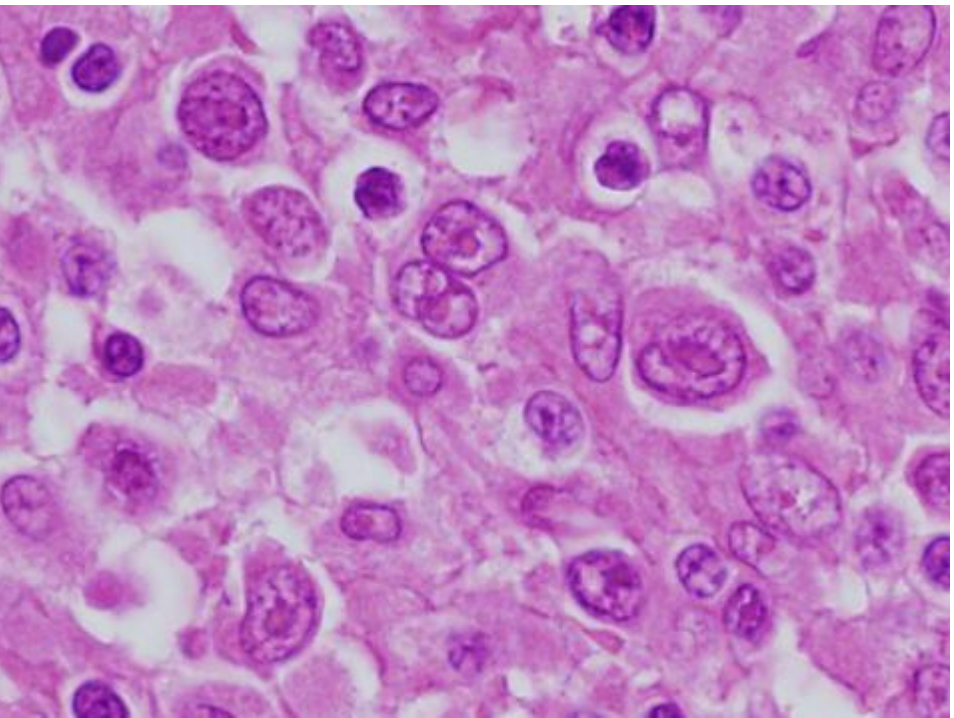
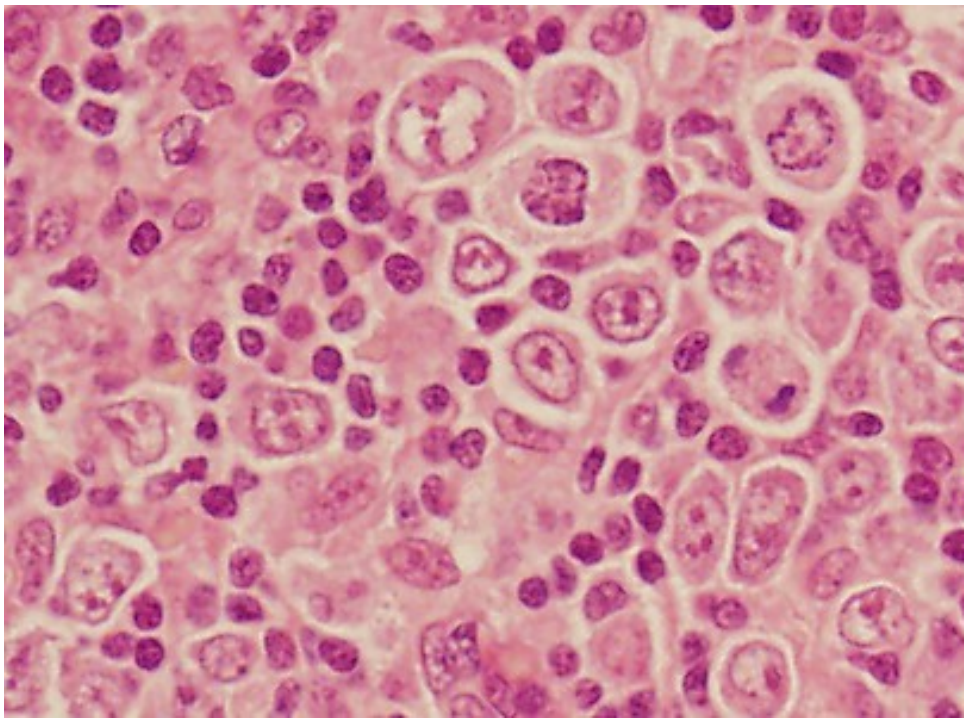
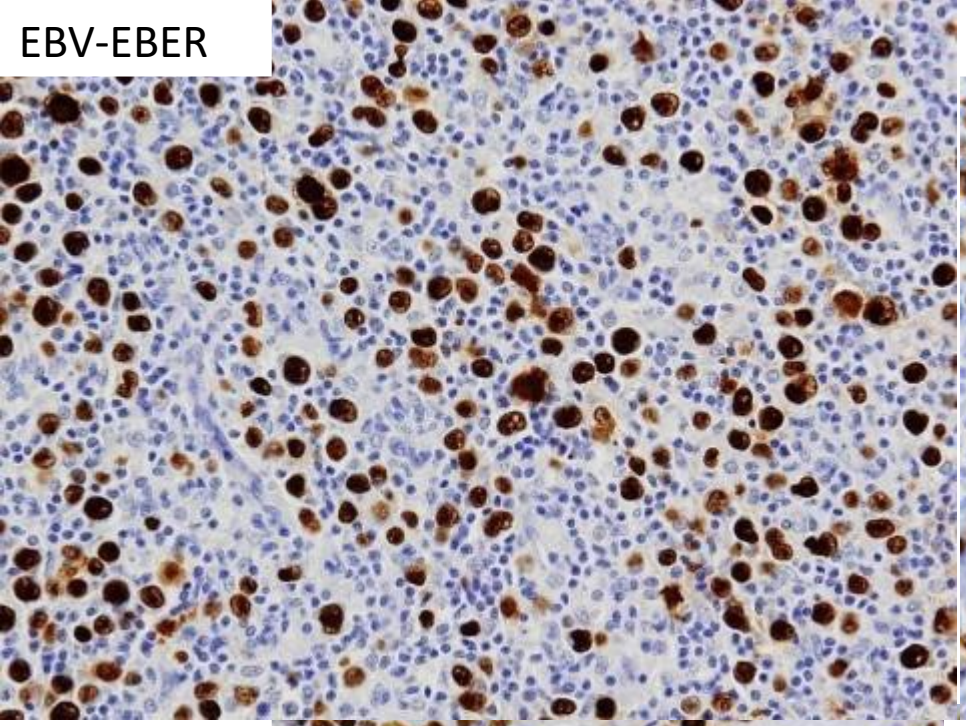
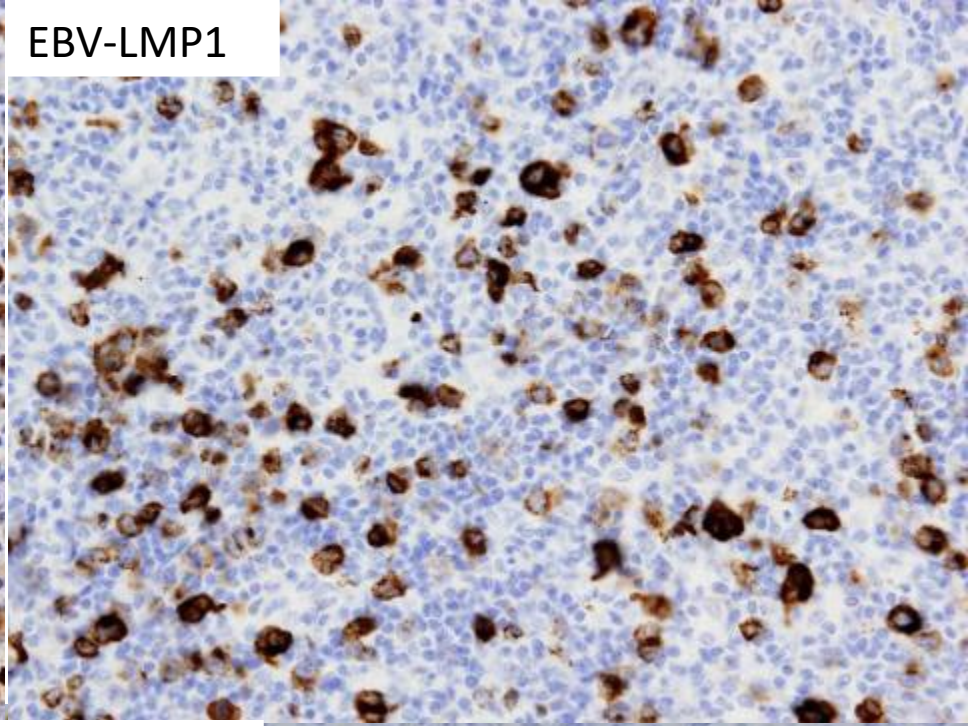
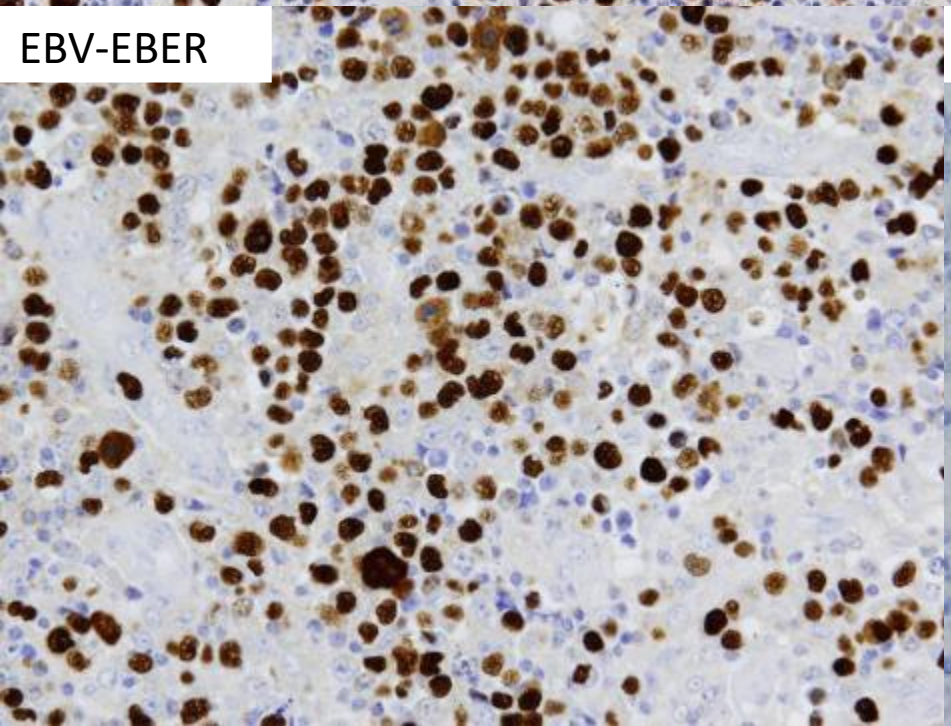


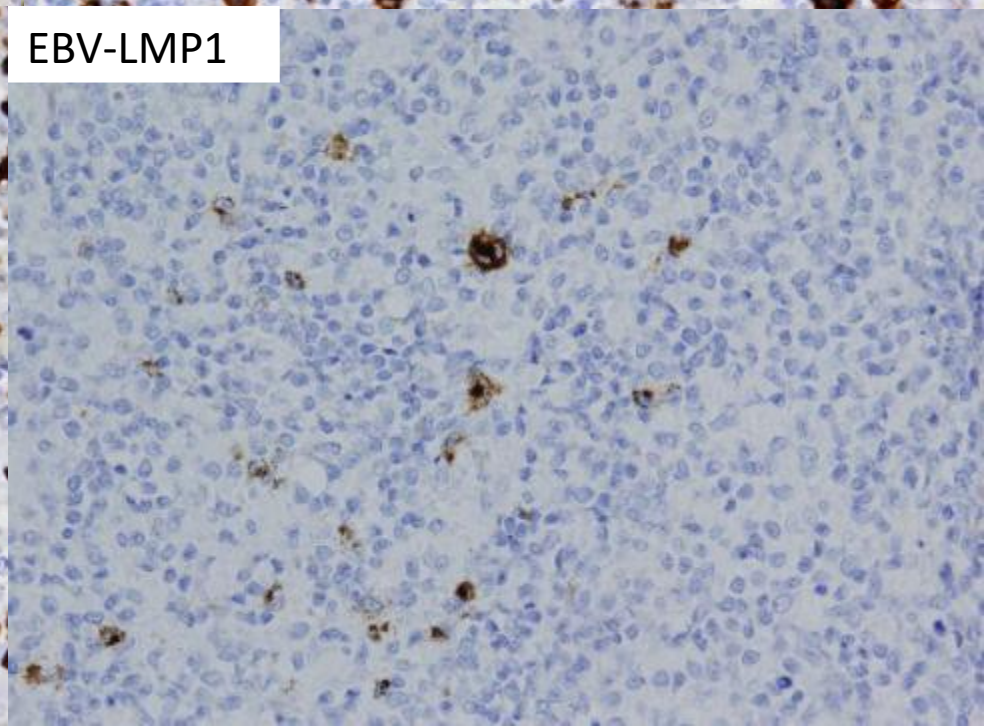





EBV-EBER


EBV-LMP1


EBV-EBER


EBV-LMP1

EBV+ DLBCL

EBV+ DLBCL in elderly patients

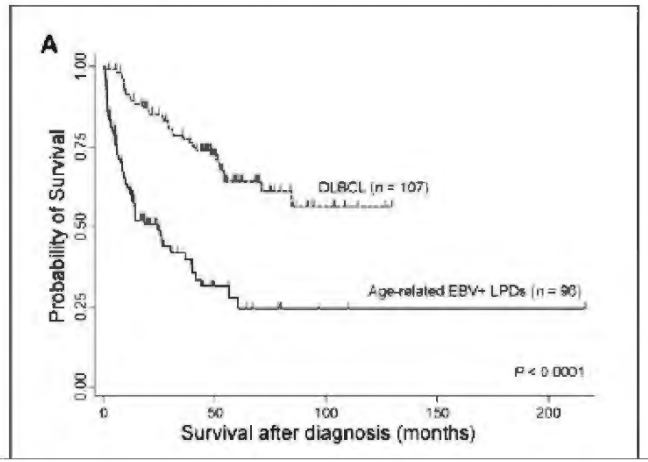
- Age > 45, 50 years
- No other causes of immunodeficiency or prior lymphoma
- More advanced stage
- More than one extranodal involvement
- Higher IPI risk group
- Poorer response to initial treatment
- Variable polymorpic infiltrate, necrosis

EBV+ large cell lymphoma are excluded from this category, if

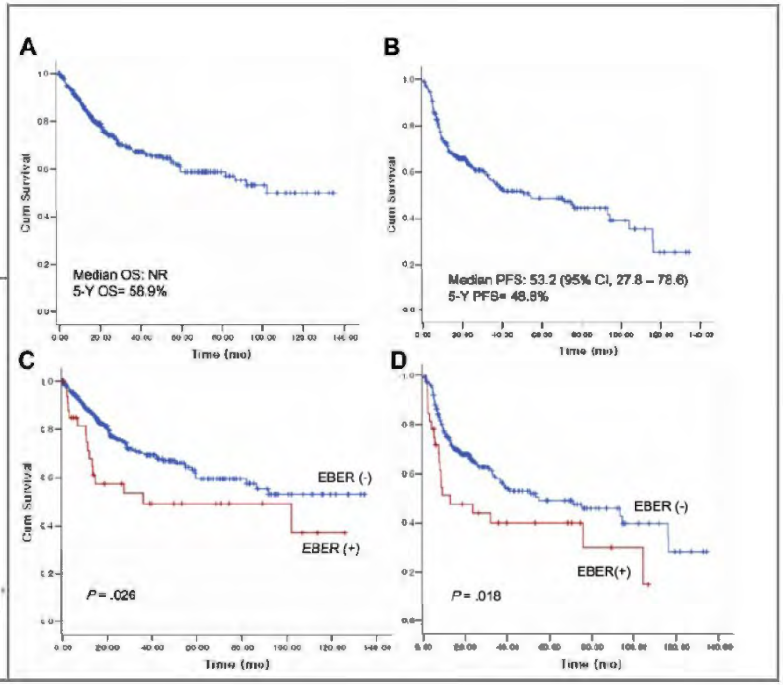
- Associated with chronic inflammation
- LyG, PBL, PEL

Age-Related EBV-Associated B-Cell Lymphoproliferative Disorders Constitute a Distinct Clinicopathologic Group: A Study of 96 Patients

Takashi Oyama,[1] Kazuhito Yamamoto,[2] Naoko Asano,[3] Aya Oshiro,[3] Ritsuro Suzuki,[4] Yoshitoyo Kagami,[2] Yasuo Morishima,[2] Kengo Takeuchi,[7] Toshiyuki Izumo,[9] Shigeo Mori,[8] Koichi Ohshima,[10] Junji Suzumiya,[11] Naoya Nakamura,[12] Masafumi Abe,[12] Koichi Ichimura,[13] Yumiko Sato,[13] Tadashi Yoshino,[13] Tomoki Naoe,[5] Yoshie Shimoyama,[6] Yoshikazu Kamiya,[1] Tomohiro Kinoshita,[5] and Shigeo Nakamura[6]



Clin Cancer Res 2007;13(17) September 1, 2007



blood

2007 110: 972-978
Prepublished online Mar 30, 2007;
doi:10.1182/blood-2007-01-067769

The impact of Epstein-Barr virus status on clinical outcome in diffuse large B-cell lymphoma

Sarah Park, Jeeyun Lee, Young Hyeh Ko, Arum Han, Hyun Jung Jun, Sang Chul Lee, In Gyu Hwang, Yeon Hee Park, Jin Seok Ahn, Chul Won Jung, Kihyun Kim, Yong Chan Ahn, Won Ki Kang, Keunchil Park and Won Seog Kim

blood

Prepublished online March 8, 2011;
doi:10.1182/blood-2010-12-323238

Age related EBV associated lymphoproliferative disorder – a spectrum of reactive lymphoid hyperplasia and lymphoma: the Western experience

Stefan D Dojcinov, Girish Venkataraman, Stefania Pittaluga, Iwona Wlodarska, Jeffrey A Schrager, Mark Raffeld, Robert K Hills and Elaine S Jaffe

MODERN PATHOLOGY (2012), 1–15
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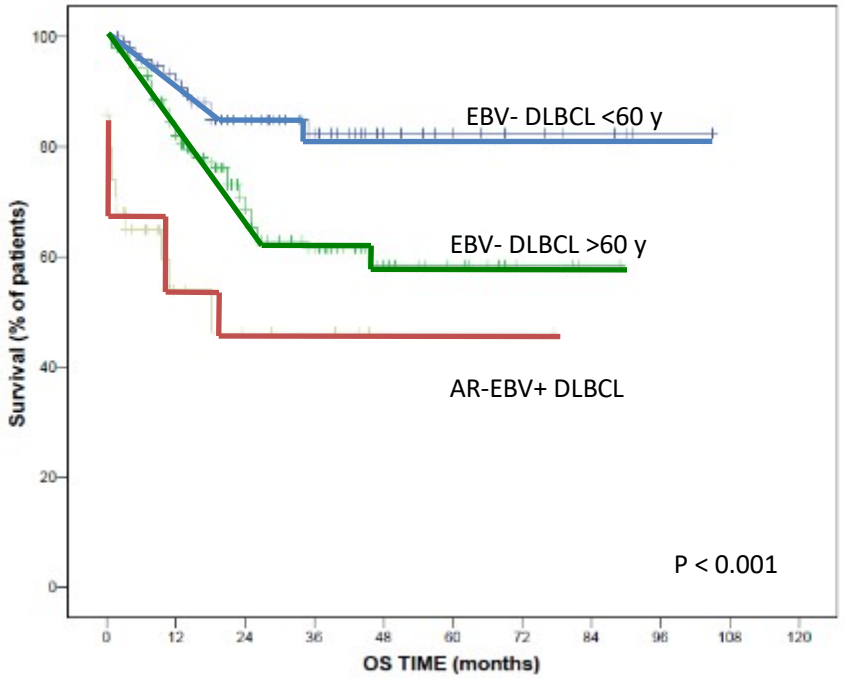
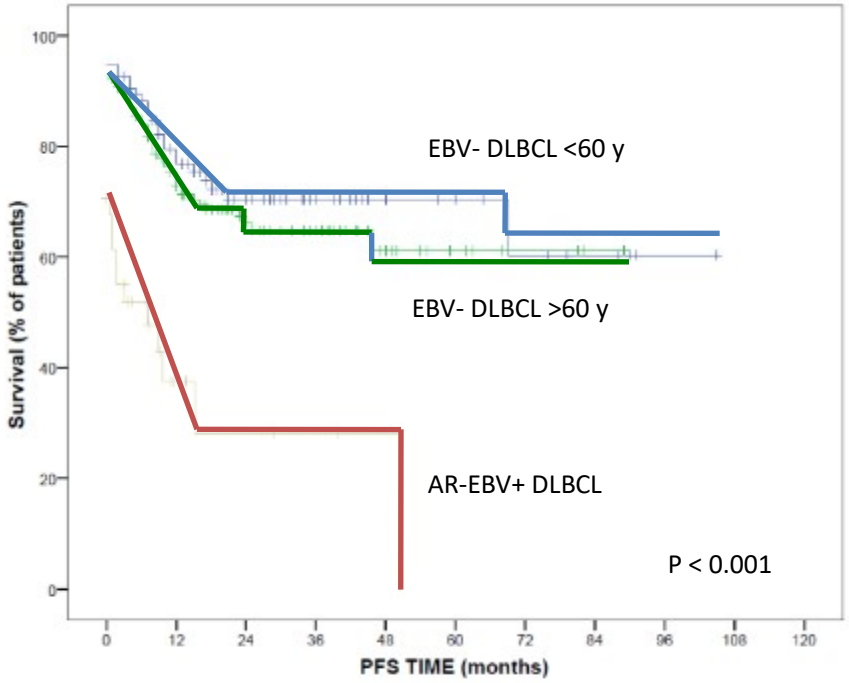
EBV-positive diffuse large B-cell lymphoma of the elderly is an aggressive post-germinal center B-cell neoplasm characterized by prominent nuclear factor-kB activation

Santiago Montes-Moreno[1], Lina Odqvist[2], Julio Alexander Diaz-Perez[3], Ana Batlle Lopez[1], Sonia Gonzalez de Villambrosía[1], Francisco Mazorra[1], Maria E Castillo[2], Mar Lopez[2], Raquel Pajares[4], Juan F García[5], Manuela Mollejo[6], Francisca I Camacho[7], Carmen Ruiz-Marcellán[8], Magdalena Adrados[9], Nazario Ortiz[10], Renato Franco[11], Carlos Ortiz-Hidalgo[12], Ana Suarez-Gauthier[13], Ken H Young[14] and Miguel A Piris[1]

Survival estimates
Age related AR-EBV+ DLBCL vs EBV- DLBCL control series



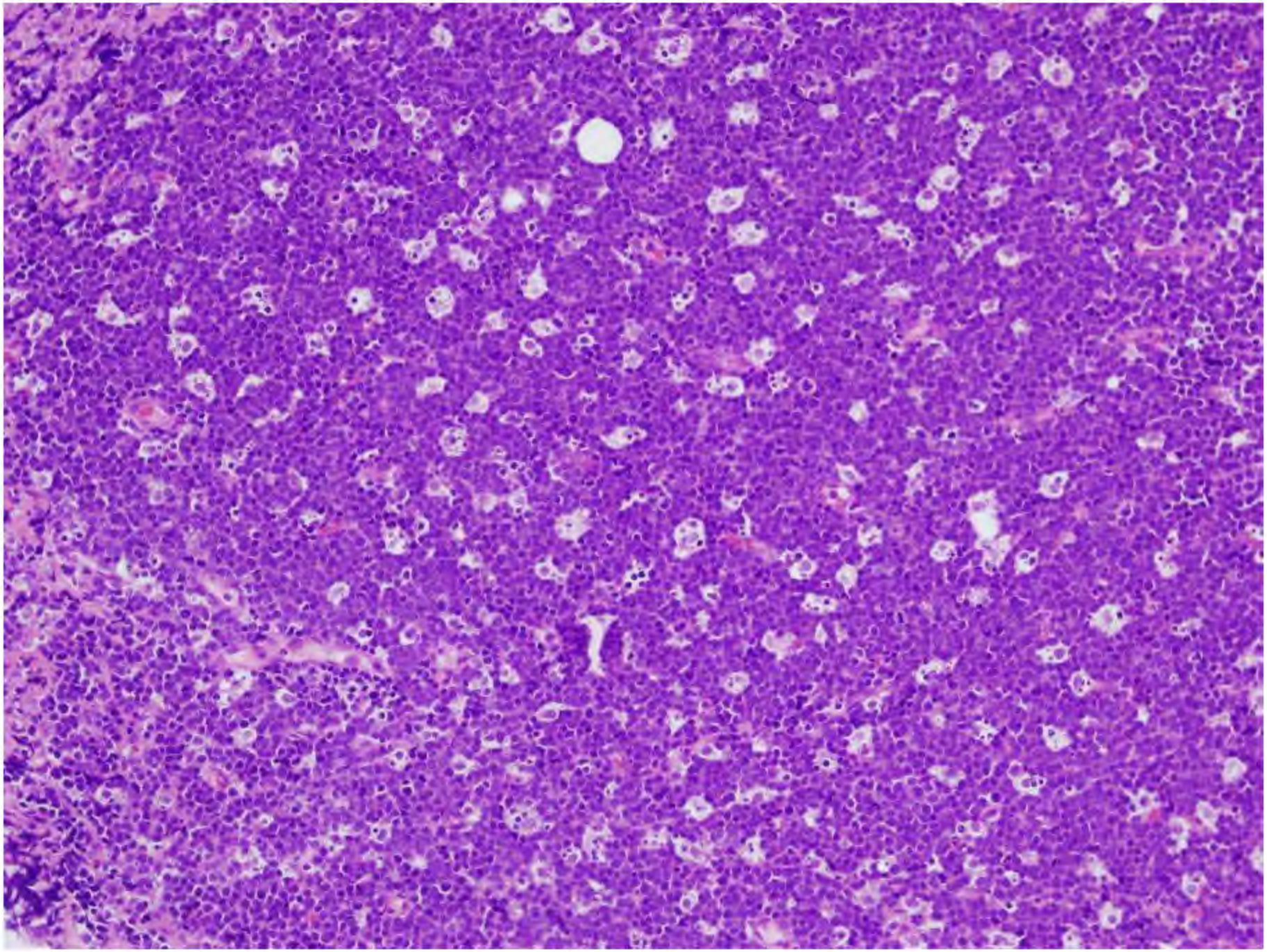


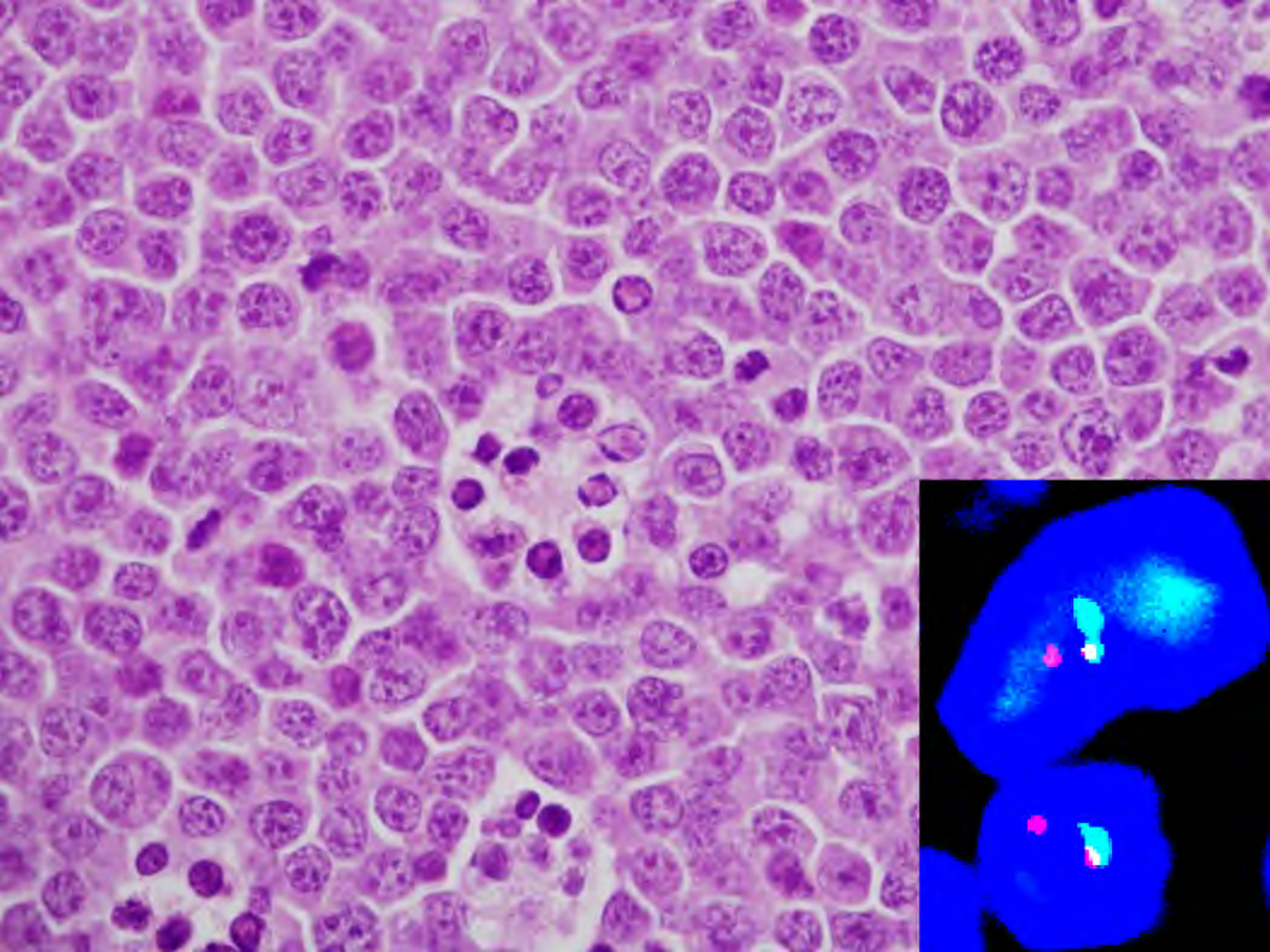
EBV+	0	12	24	36	48	60	72	84	96	108	120
N patients at risk	35	8	5	4	1	1	1	0	0	0	0
EBV- < 60y	0	12	24	36	48	60	72	84	96	108	120
N patients at risk	95	70	47	29	12	8	6	4	1	0	0
EBV- > 60y	0	12	24	36	48	60	72	84	96	108	120
N patients at											

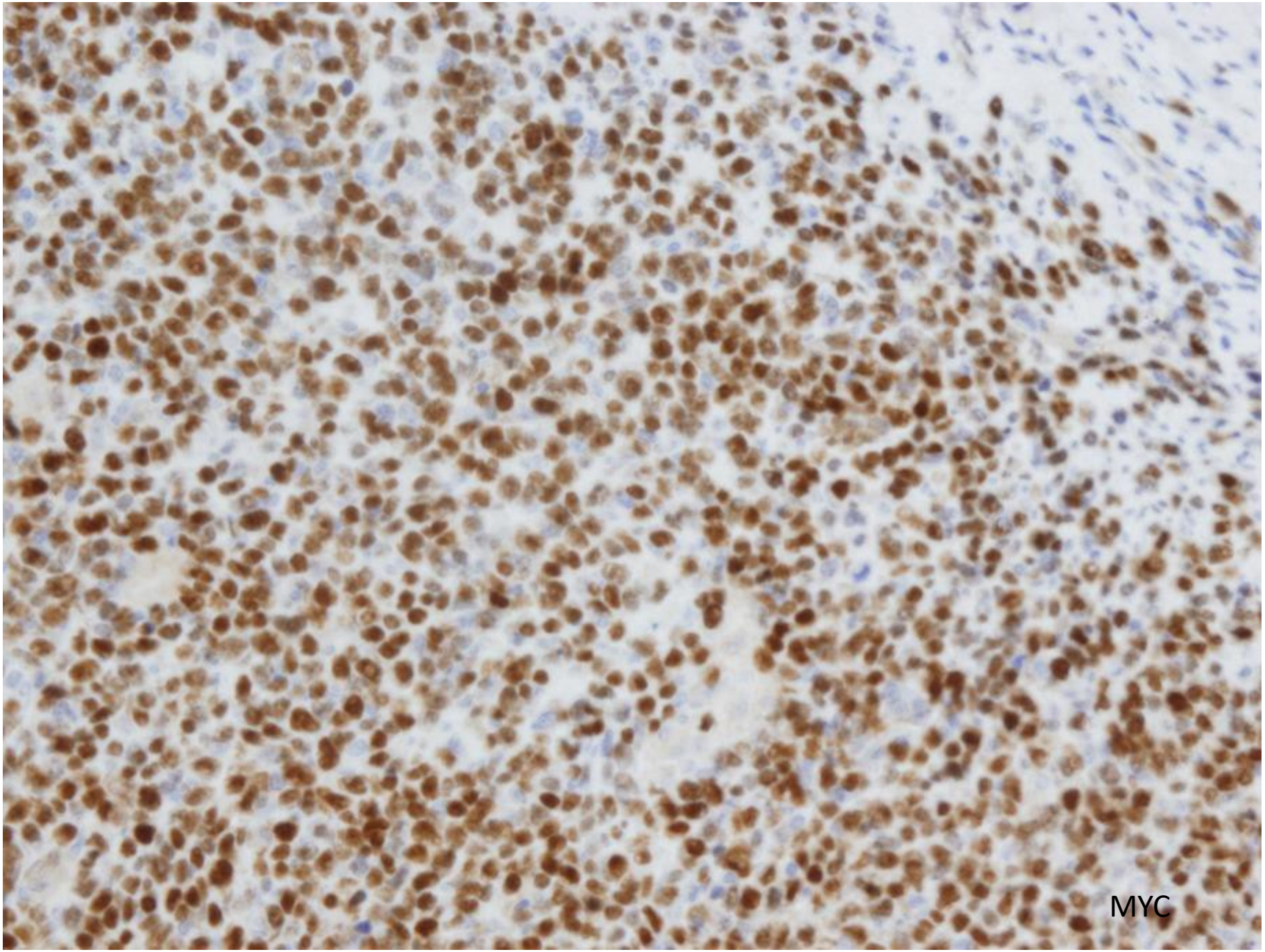
EBV+	0	12	24	36	48	60	72	84	96	108	120
N patients at risk	34	5	3	2	1	0	0	0	0	0	0
EBV- < 60y	0	12	24	36	48	60	72	84	96	108	120
N patients at risk	95	58	37	21	10	8	6	4	1	0	0
EBV- > 60y	0	12	24	36	48	60	72	84	96	108	120
N patients at											

Case 3

HIV+ 35 yrs old female
Cervical lymphadenopathy






MYC

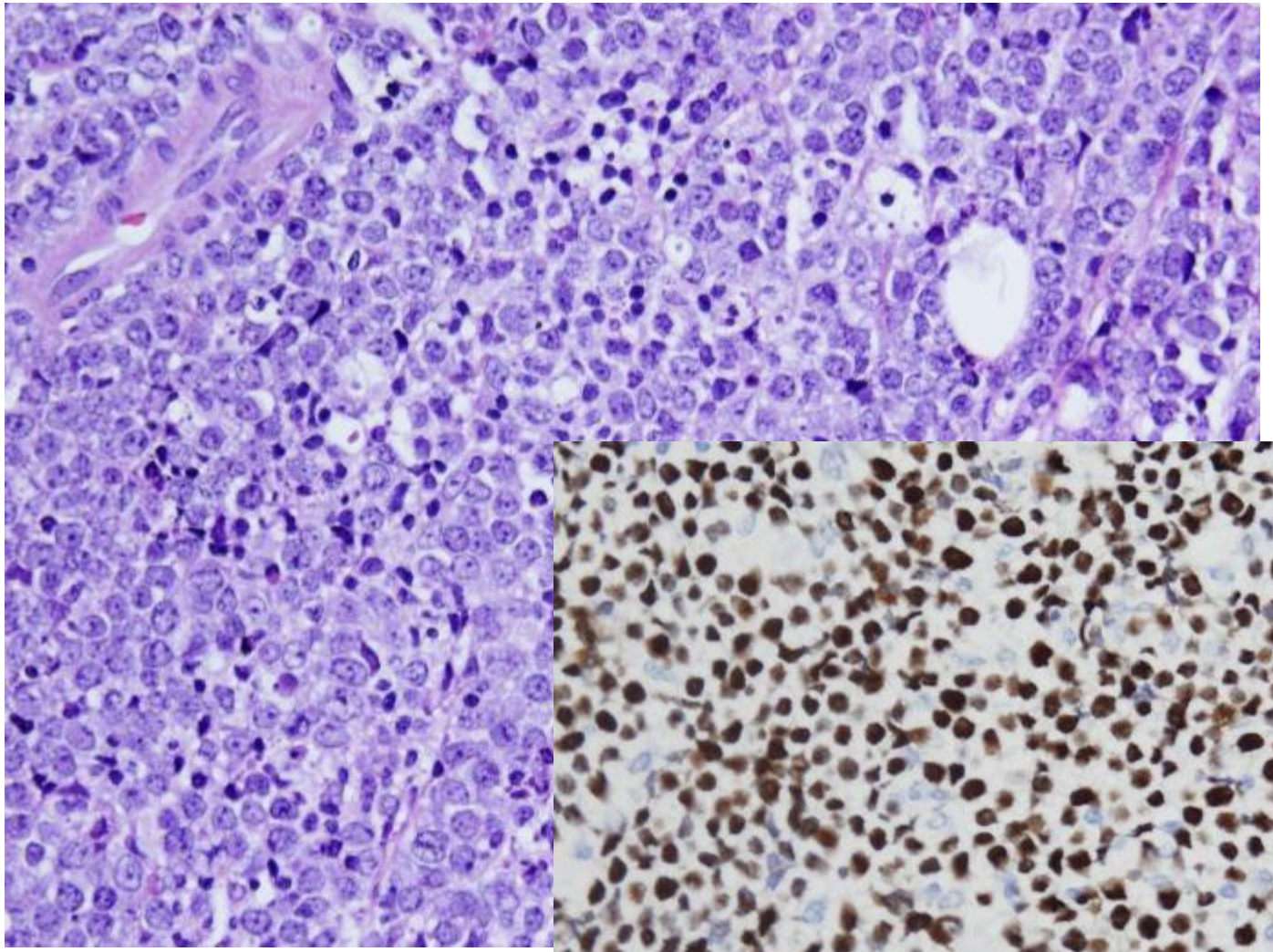
Burkitt Lymphoma

Burkitt Lymphoma

Fig. 10.121 Endemic Burkitt lymphoma. This African patient presented with a large jaw tumour.

Fig. 10.122 Sporadic Burkitt lymphoma with bilateral ovarian tumours.

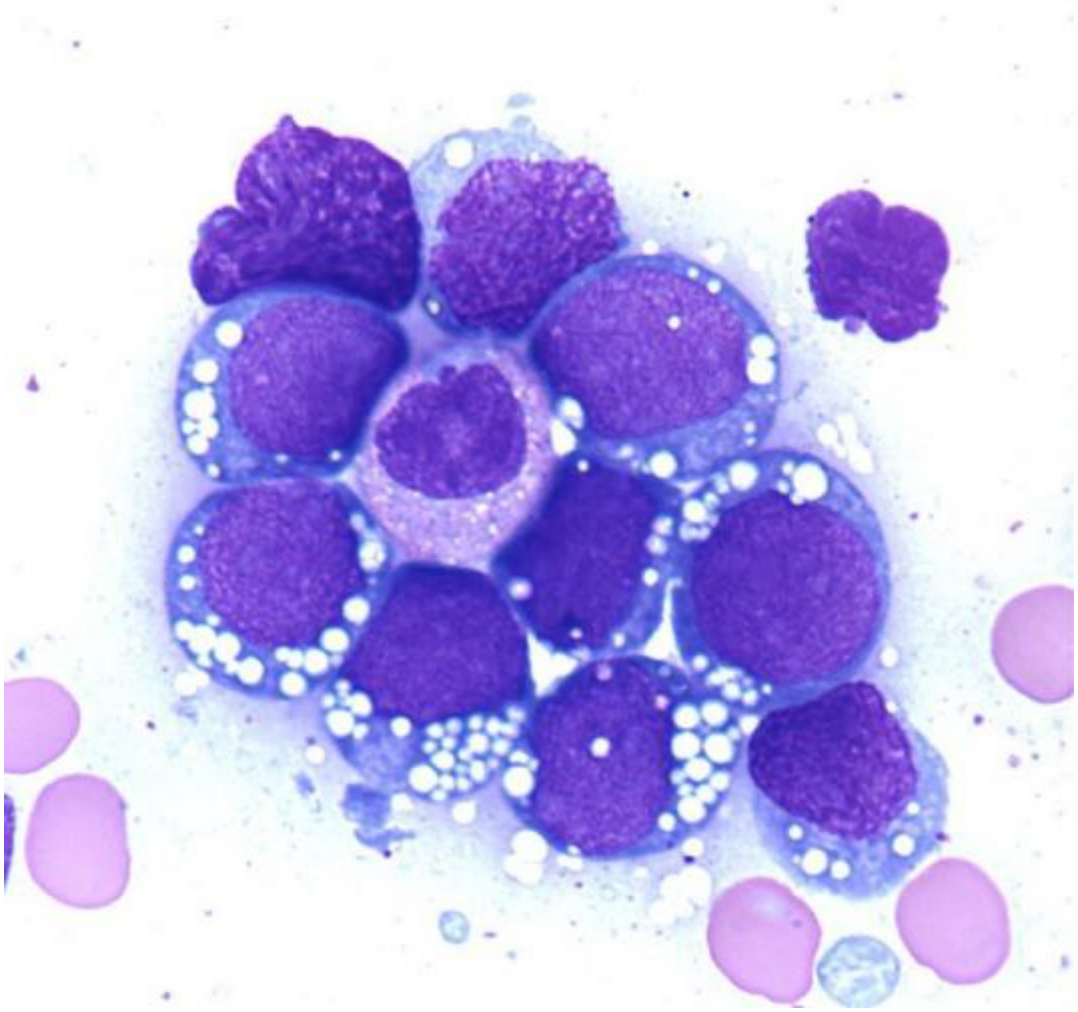
Fig. 10.123 Bilateral breast involvement may be the presenting manifestation during pregancy, and puberty. BL cells have prolactin receptors.



Burkitt Lymphoma

- t8;14 positive medium size B-cell lymphoma, with Ki67>90%
- Frequent extranodal presentation, intestinal, ovarian,….
- 2nd decade, but can be seen at any age
- Characteristic morphological features, starry-sky, medium-size cytology,….
- CD20+ CD10+ Tdt-
- Most cases are BCL2-, but some may be positive
- EBV+ in endemic forms, HIV and immunodeficiency
- Other C-MYC translocations: peculiar features

Burkitt leukemia - 3.



Peter Maslak, ASH Image Bank 2011; 2011-1118

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C-MYC translocation

- t8;14 involving IGH and C-MYC is typical for Burkitt, classical
- Can be seen in other B-cell lymphomas, such as

  DLBCL

  Aggressive forms of FL, CLL, MCL, CLL
- In classical BL usually this is the only translocation
- Is usually associated with increased C-MYC expression detectable by IHC
- C-MYC expression can be deregulated through alternative mechanisms
- Translocations involving IGK or IGL and C-MYC are more typical for other B-cell lymphoma
- Cases lacking t8;14 may carry alternative chromosomal alterations, like 11q

Julio Finalet Ferreiro,[1] Julie Morscio,[2] Daan Dierickx,[3] Lukas Marcelis,[2] Gregor Verhoef,[3] Peter Vandenberghe,[1] Thomas Tousseyn,[2] and Iwona Wlodarska[1]

[1]KU Leuven, University of Leuven, Center for Human Genetics; [2]KU Leuven, University of Leuven, Translational Cell and Tissue Research and KU Leuven, University Hospitals Leuven, Department of Pathology; and [3]KU Leuven, University Hospitals Leuven, Department of Hematology, Belgium

Post-transplant molecularly defined Burkitt lymphomas are frequently *MYC*-negative and characterized by the 11q-gain/loss pattern

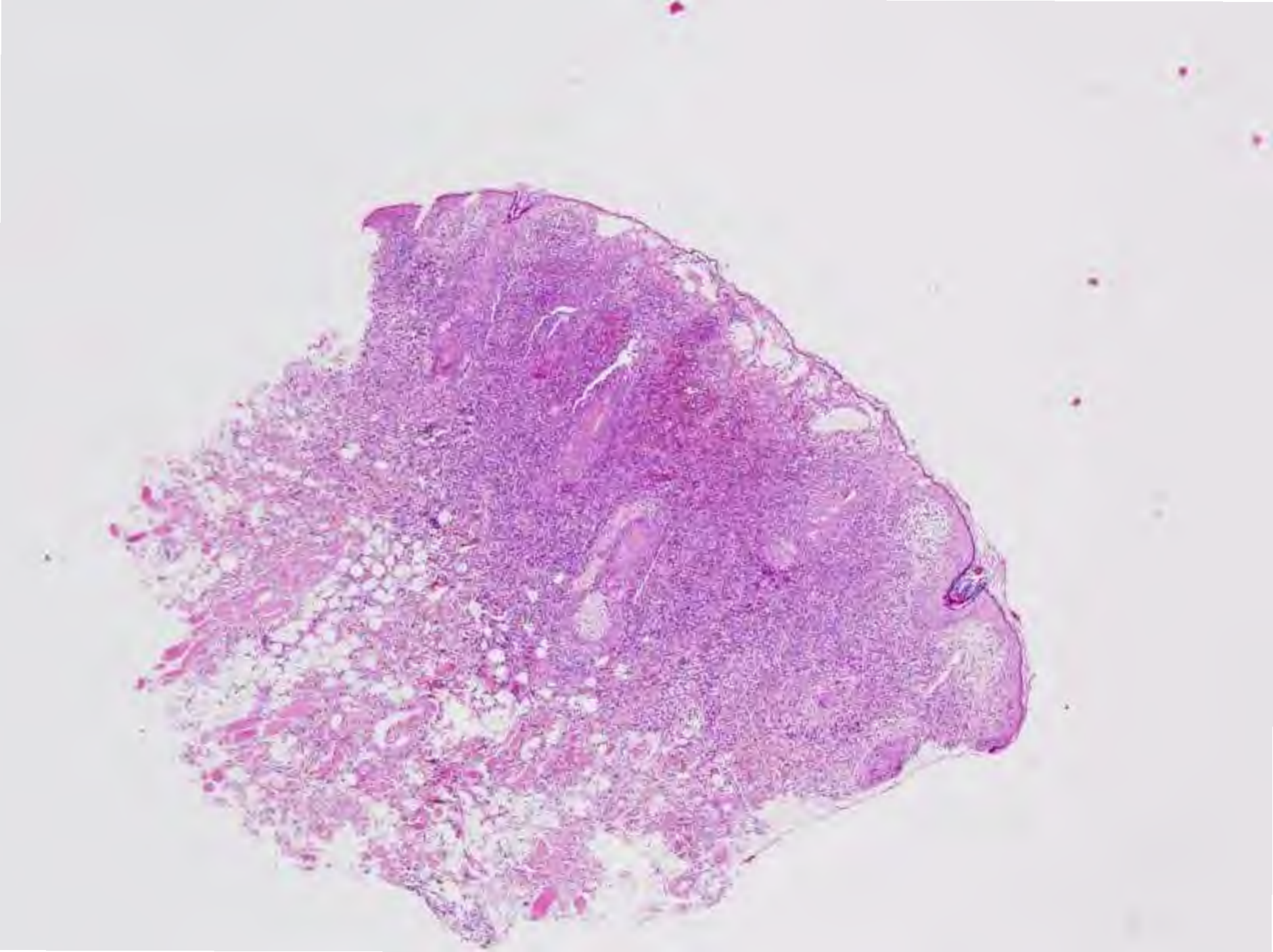
Table 1. Morphology and immunophenotype of the reported post-transplant and immunocompromised BL cases.

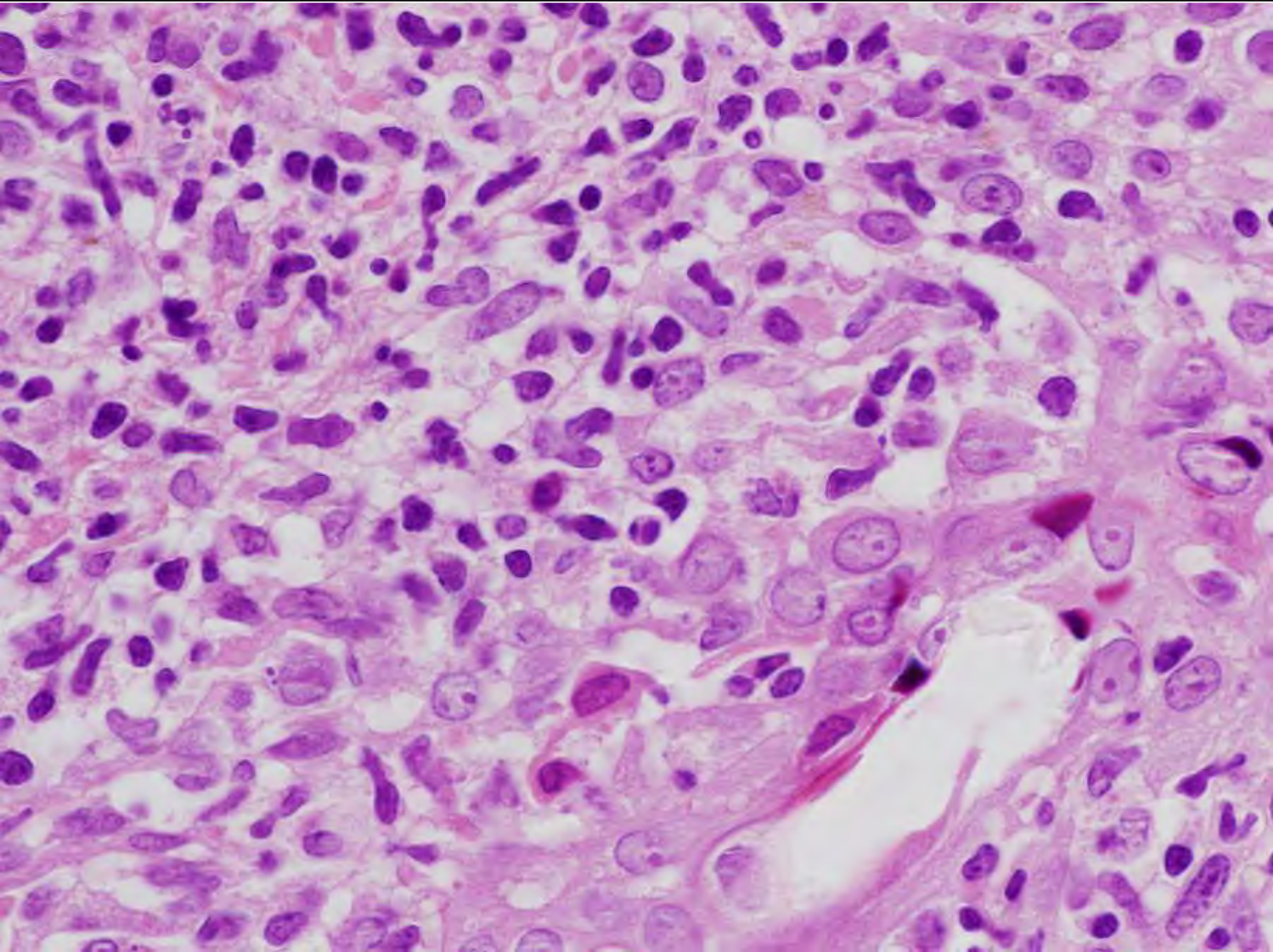
Case	Localization	Morphology	Immunohistochemistry									EBV latency profile
			CD20	CD10	MYC (%)	TdT	BCL2	BCL6	MUM1	KI67 (%)	EBER	
***MYC*-translocation-positive PT-mBL**												
1	LN	medium and large-sized cells, limited starry sky	pos	pos	0		pos*	pos	neg	100	neg	
2	LN	large-sized cells, starry sky	pos	pos	35	neg	neg	pos	neg	100	neg	
3	GALT	medium-sized cells, starry sky	pos	pos	100		neg	pos	neg	95	pos	intermediate
4	LN	medium-sized cells, starry sky	pos	pos	100	neg	neg	pos	neg	95	pos	intermediate
***MYC*-translocation-negative PT-mBL**												
5	WR	large-sized cells, starry sky	pos	pos	0	neg	neg	pos	neg	90	neg	
6	LN	medium-sized cells, starry sky	pos	pos	25 (w)	neg	neg	pos	neg	99	neg	
7	T	large-sized cells, starry sky	pos	pos	75 (w)		neg	pos	neg	99	neg	
***MYC*-translocation-positive IC-mBL**												
8	GALT	large-sized cells, starry sky	pos	pos	50	neg	neg	pos	pos	100	neg	
9	LN	medium-sized cells, starry sky	pos	pos	90	neg	neg	pos	pos	100	neg	
10	LN	medium-sized cells, limited starry sky	pos	pos	0	neg	neg	pos	neg	90	neg	
11	LN	medium-sized cells, starry sky	pos	pos	25	neg	neg	pos	neg	95	neg	

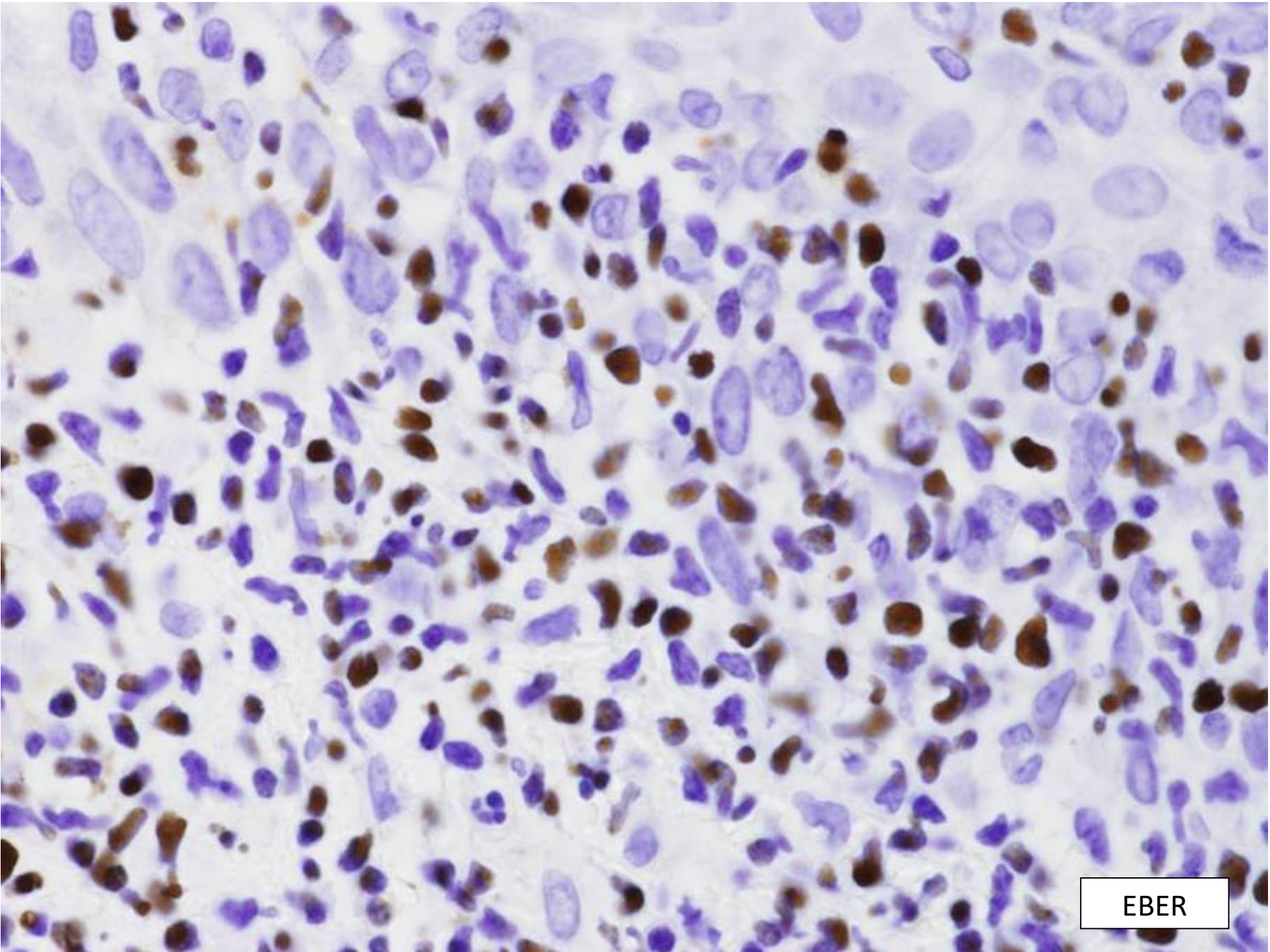
**Normal FISH BCL2 pattern; PT: post-transplant; IC: immunocompetent; mBL: molecular Burkitt lymphoma; LN: lymph node; GALT: gut associated lymphoid tissue; WR: Waldeyer ring; T: testis; pos: positive; neg: negative; w: weak.*

Case 4

6 yrs old Peruvian child
Hydroa-like disorder





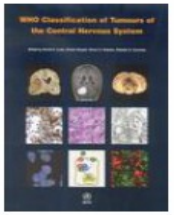

EBER

Hydroa-like lymphoproliferative disorder

Mature T-and NK-cell neoplasms - EBV

Epstein-Barr virus (EBV) positive T-cell lymphoproliferative diseases of childhood

- Systemic EBV+ T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoproliferative disorder



Medical charts of patients under 18 years of age with diagnosis of cutaneous lymphomas admitted to INEN between January 1987 and February 2009, were reviewed. Epidemiologic and clinical data were obtained.

Most frequent regions with patients with Cutaneous Lymphomas (Southern highlands)

HVLD – Clinical features

- Patients present with lesions that affects sun-exposed and to a lesser extent sun-protected areas (face and upper limbs)
- Edema, papules, blisters, crusts, ulcers and heal as vacciniform scars
- B-Symptoms
- Rare hypersensitivity to insect bites
- Lymphadenopathy (30%)
- Hepatosplenomegaly (10%)

HVLD – Clinical features

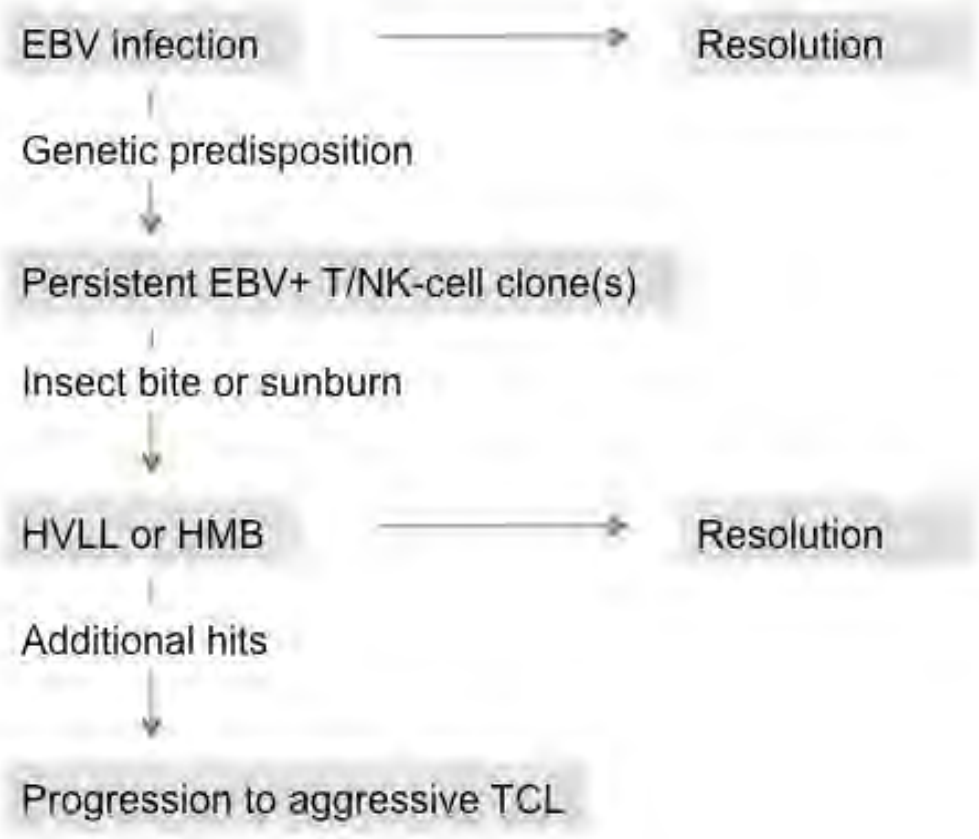
- Follow-up:
  - 10/14 deaths, 2-40 months
  - 4 alive with disease, 4-18 months
- Causes of death:
  - Progression
  - Infection
  - Haemophagocytic syndrome

HVLD – Clinical features

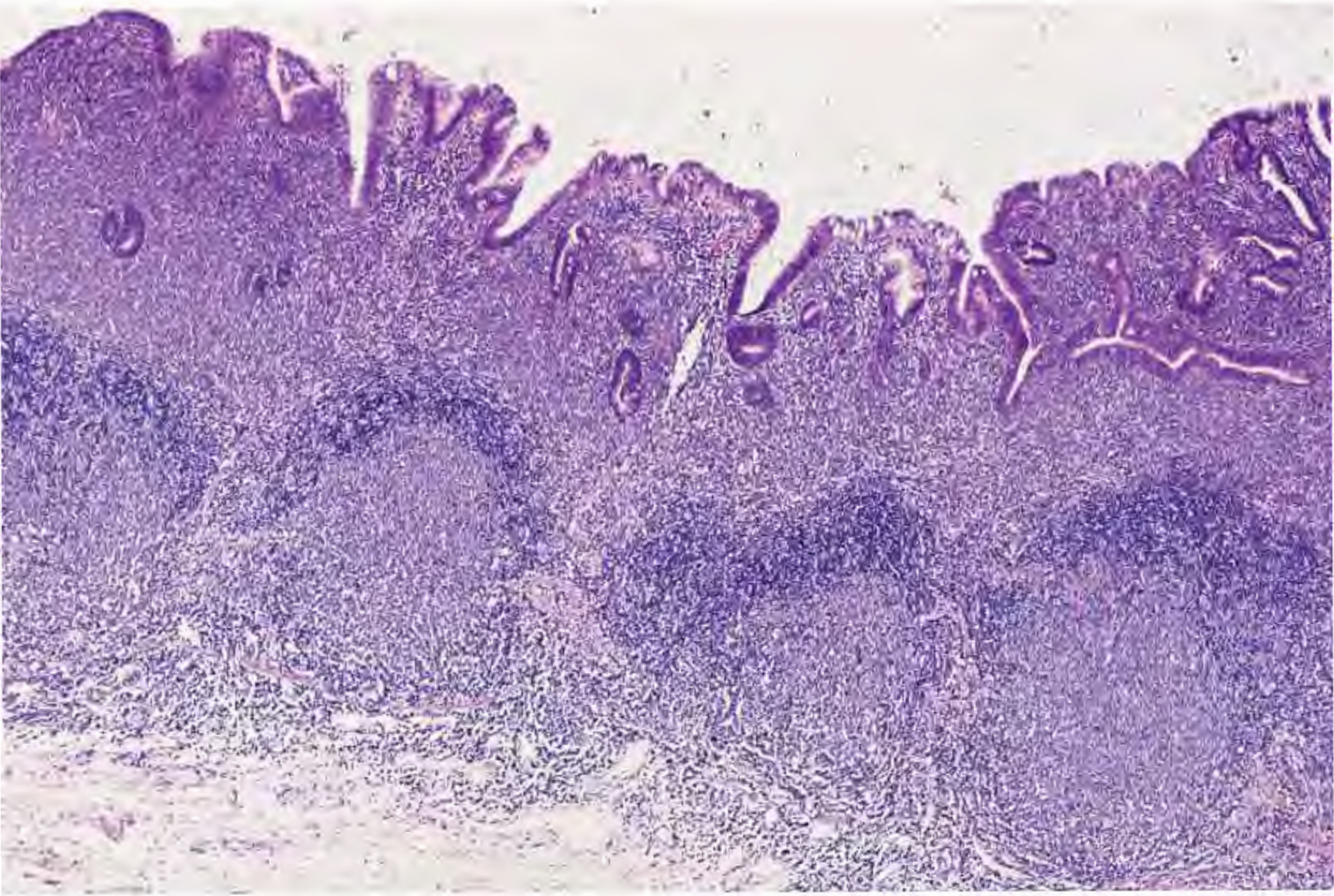
HVLD – Clinical features

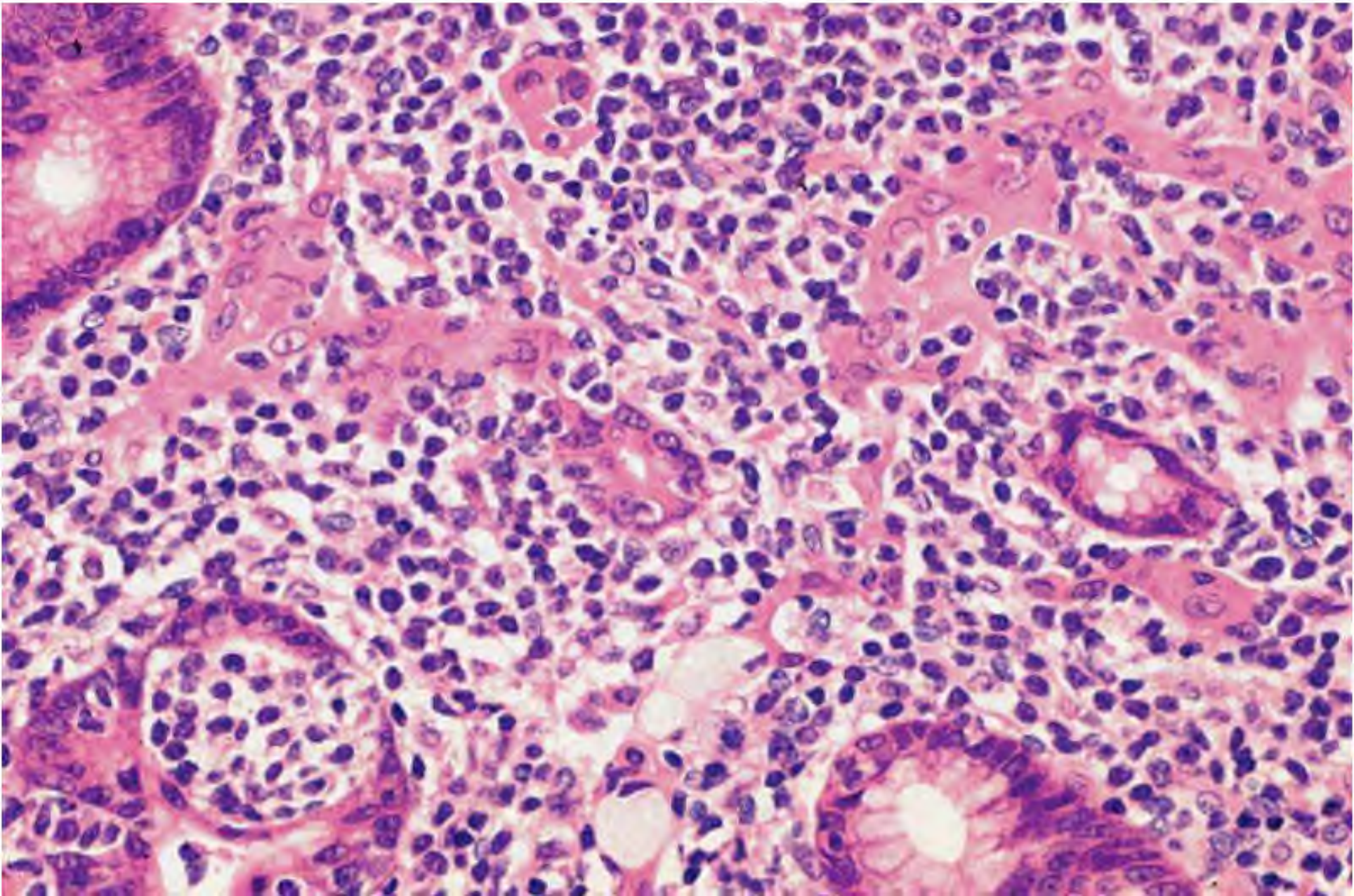
HVLD – Clinical features

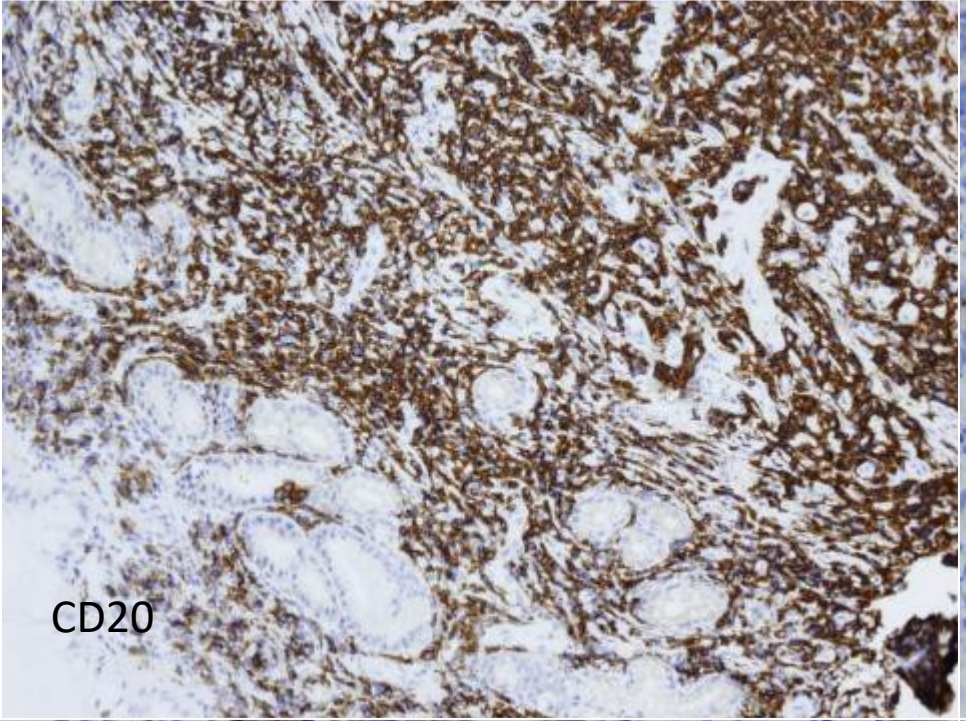
Theoretical sequence of events in chronic EBV+ lymphoproliferative disorder

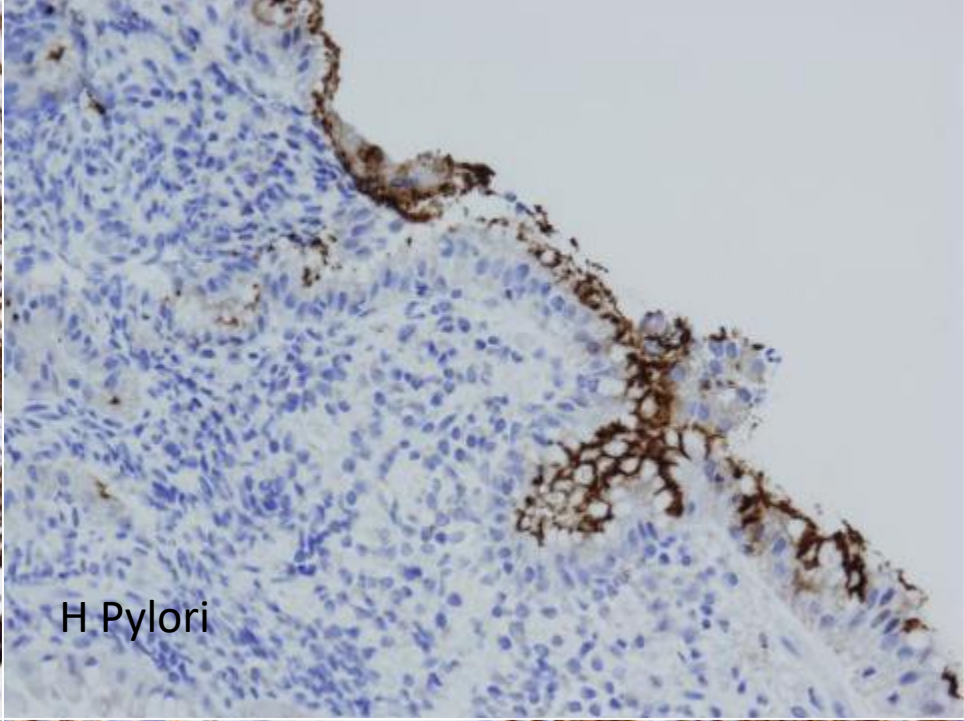


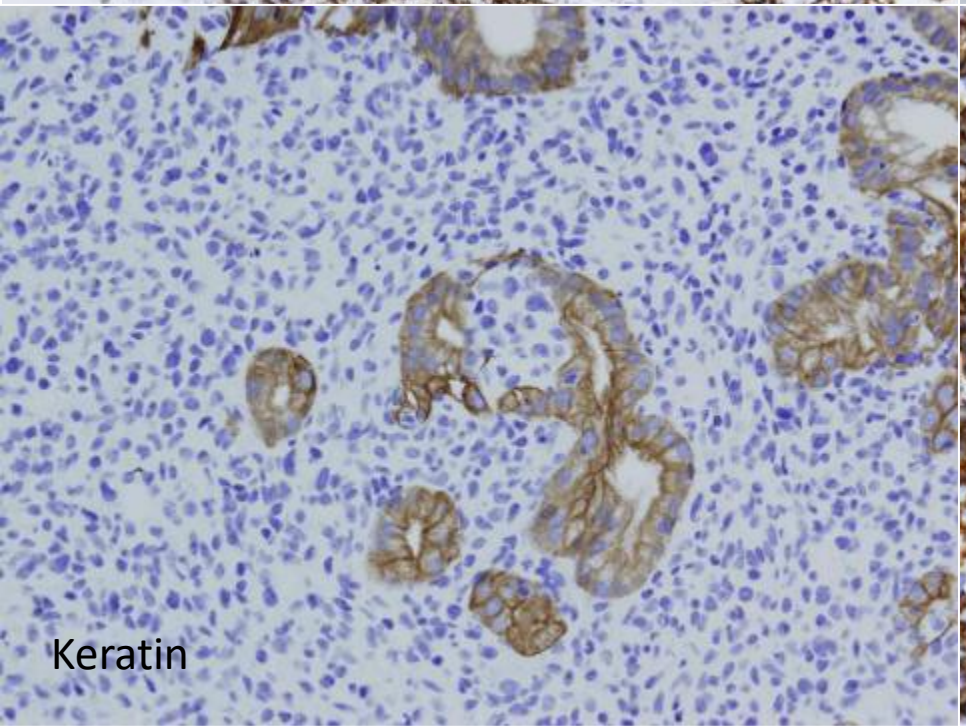
Case 5

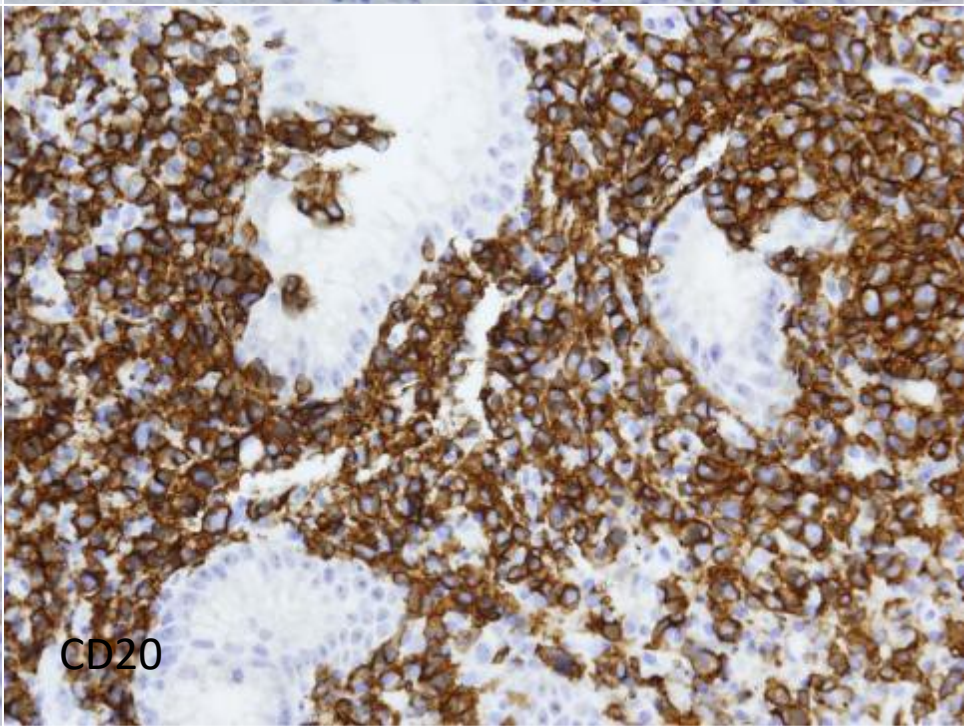


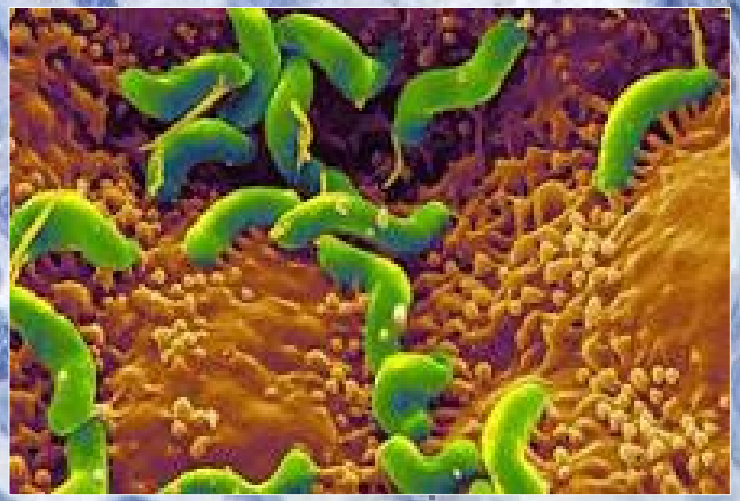



CD20


H Pylori


Keratin


CD20



Marginal zone B-cell lymphoma, MALT-type

H Pylori infection
from gastritis to MALT lymphoma

Marginal zone lymphoma - MALT

- Accumulation of extranodal lymphoid tissue is the primary event in MALT lymphoma following the development of an inflammatory site in response to chronic infection or autoimmune disorders.

- Translocations involving genes regulating NF-kB activation after B-cell receptor signalling (MALT1, API2, BCL10) are characteristic of this neoplasm. These translocations are site-specific, emphasizing the role of tissue-specific factors in the genesis of this neoplasm.

- NF-kB-negative regulation, provided by TNFAIP3, is lost by genetic deletion and inactivating mutations, preferentially in MALT lymphoma cases lacking chromosome translocations.

Marginal zone lymphoma - MALT

- Neoplastic cells carry on a high level of IgH somatic mutation, with a bias toward the use of V(H) gene segments.
- MZL-MALT cases with chromosomal translocations are independent of antigenic stimulation, whereas cases lacking chromosomal translocations require ongoing chronic inflammation for survival, provided by bacteria, virus or autoimmune disorders.
- Thus, t(11;18)-positive gastric tumors are resistant to antibiotics and are associated with advanced-stage disease.

B-cell lymphomas associated with infectious agents

- HCV:

Marginal Zone lymphoma

Other B-cell lymphoma

Monoclonal lymphocytosis +/- cryoglobulinemia

- Paludism

Marginal Zone lymphoma

Monoclonal lymphocytosis +/- cryoglobulinemia

- Helicobacter pylori,…

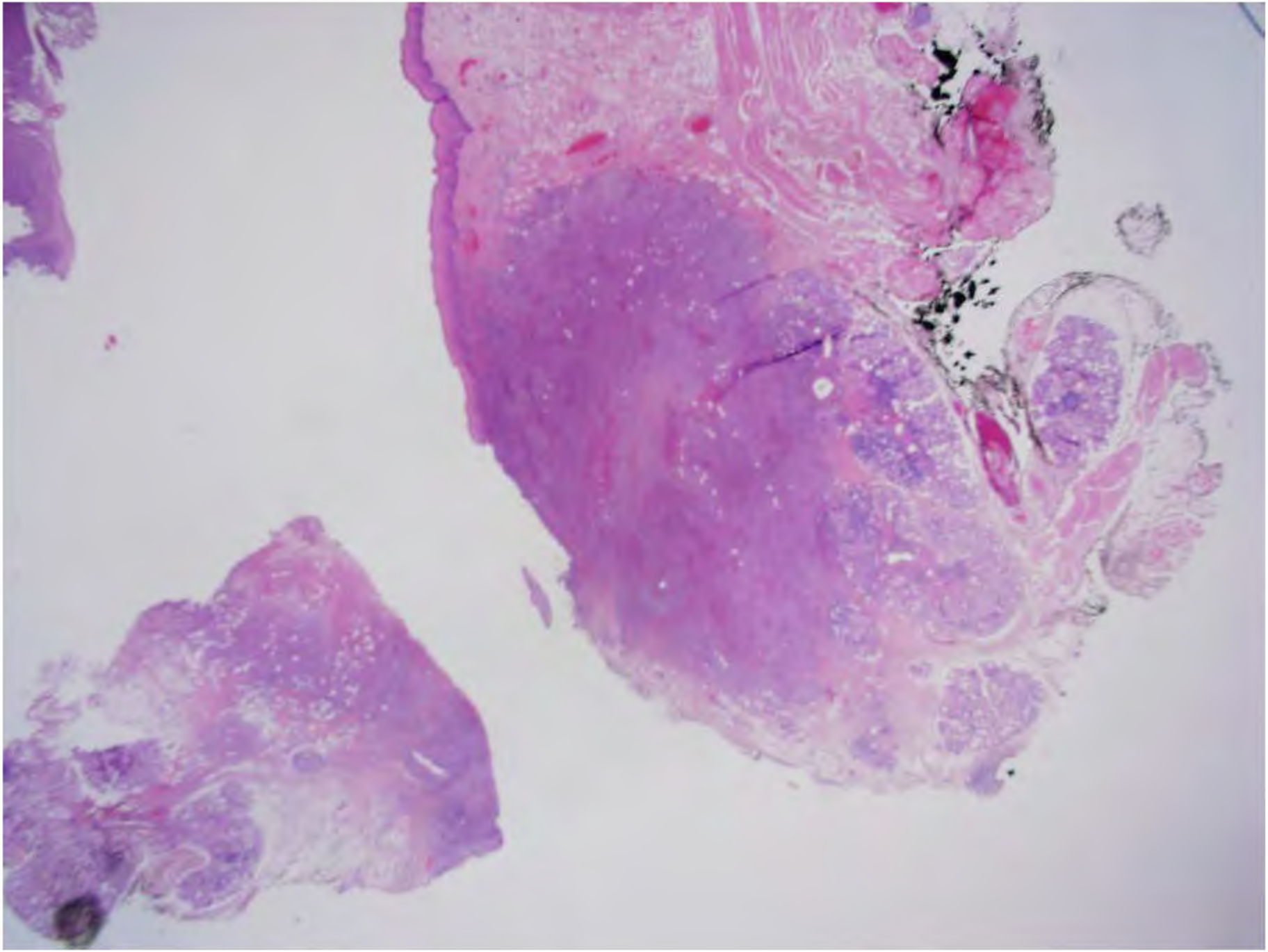
MALT lymphoma

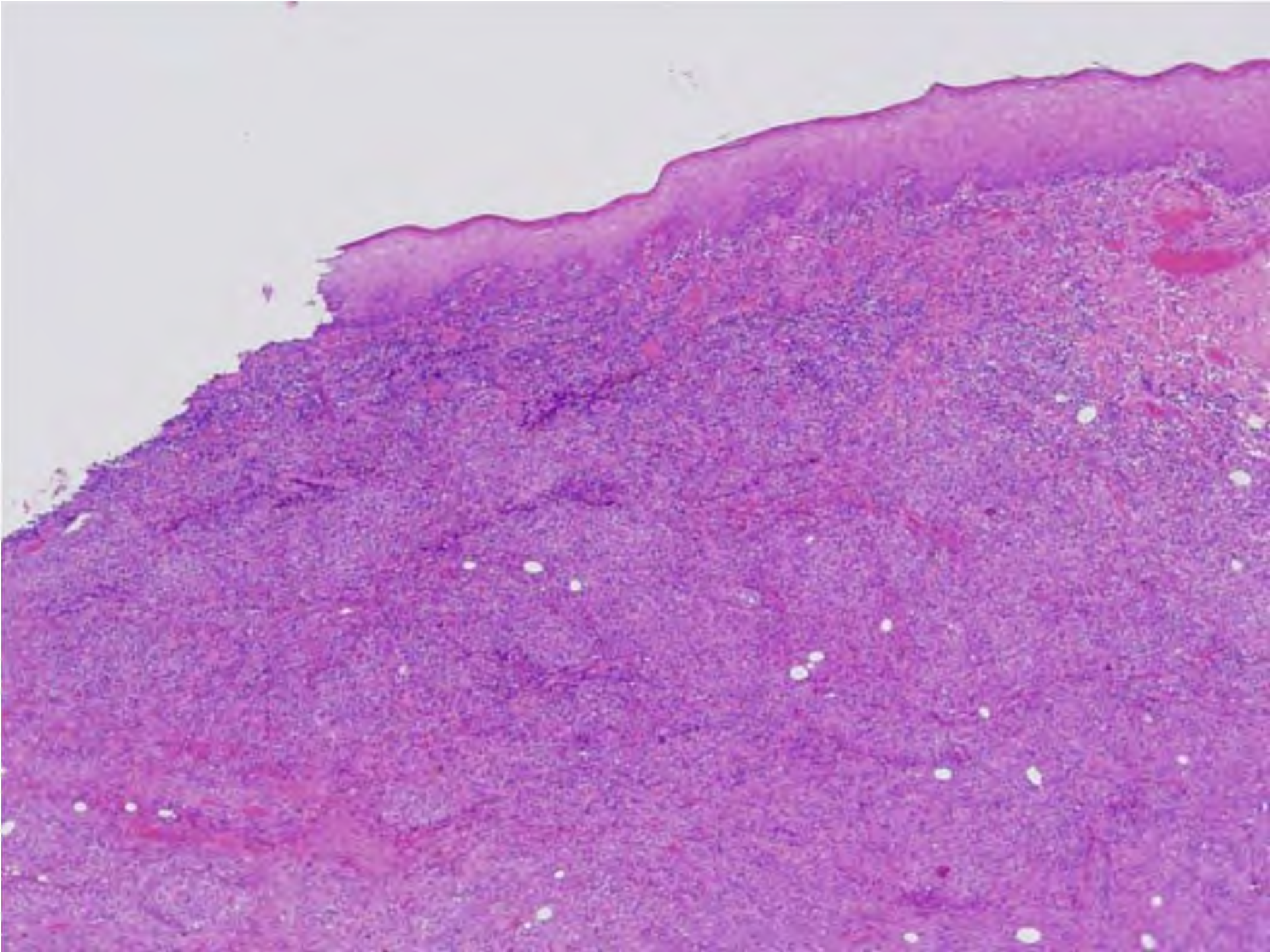
- EBV:

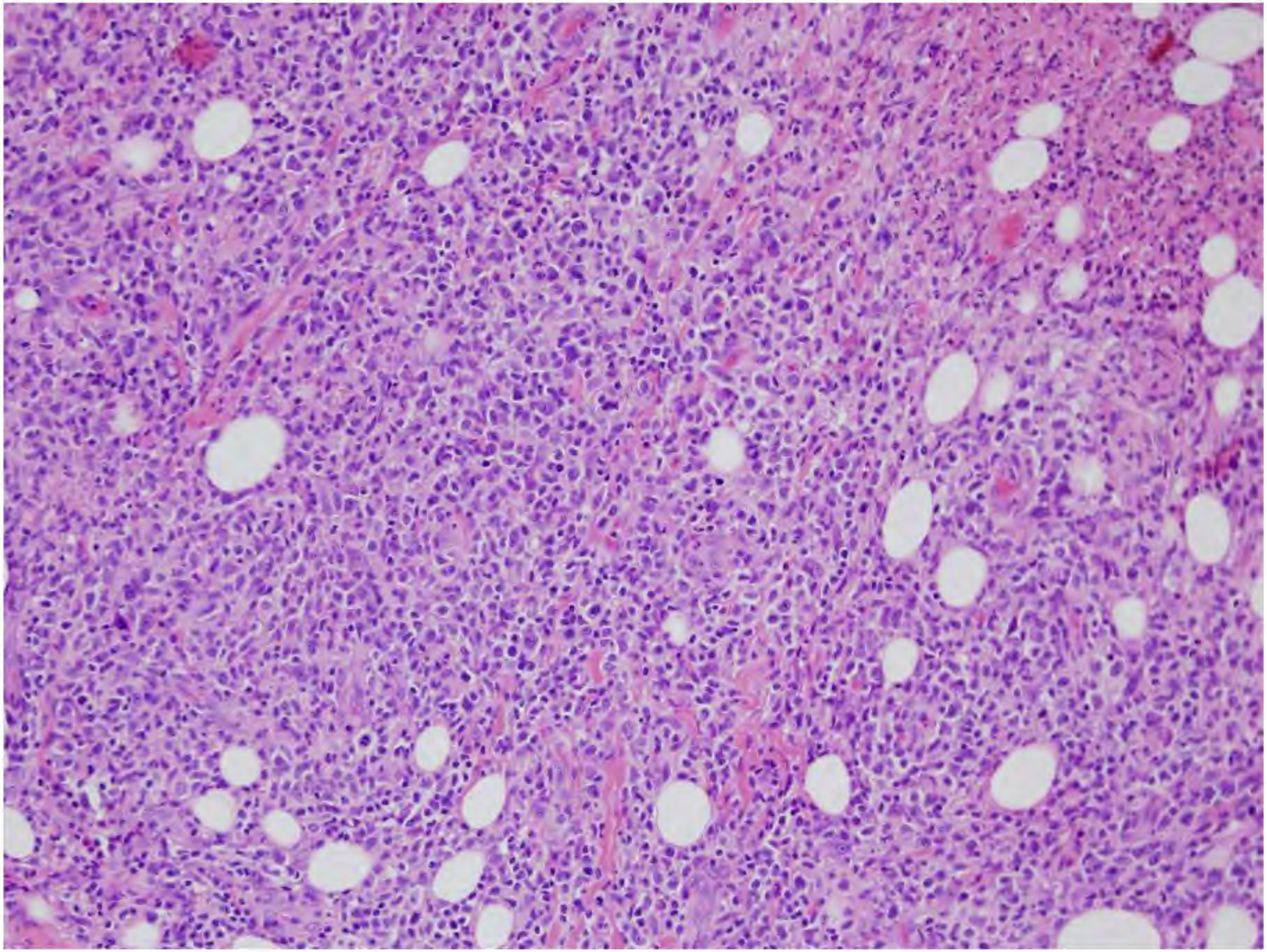
Immunodeficiencies, Immunosuppression,

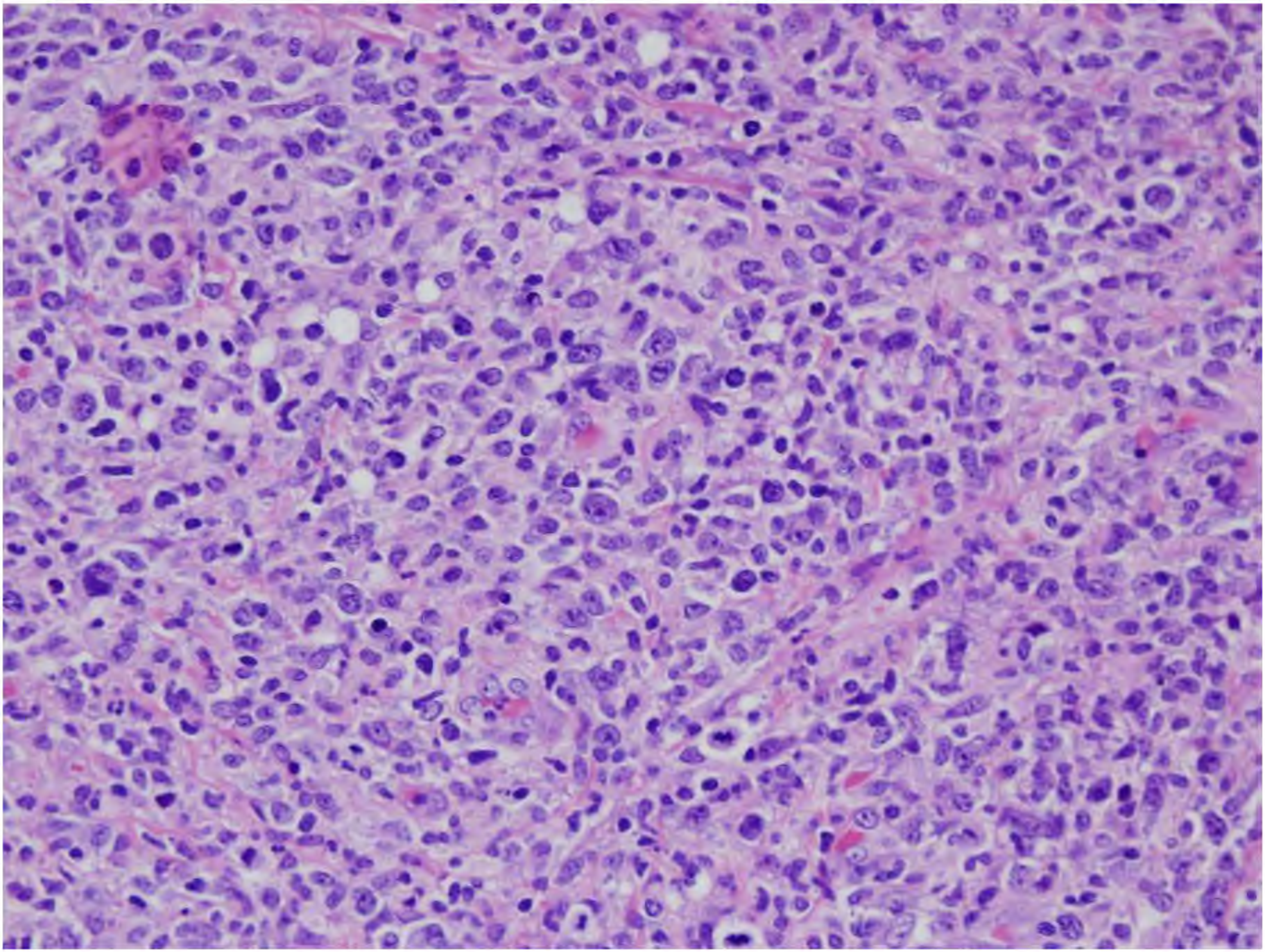
Case 6

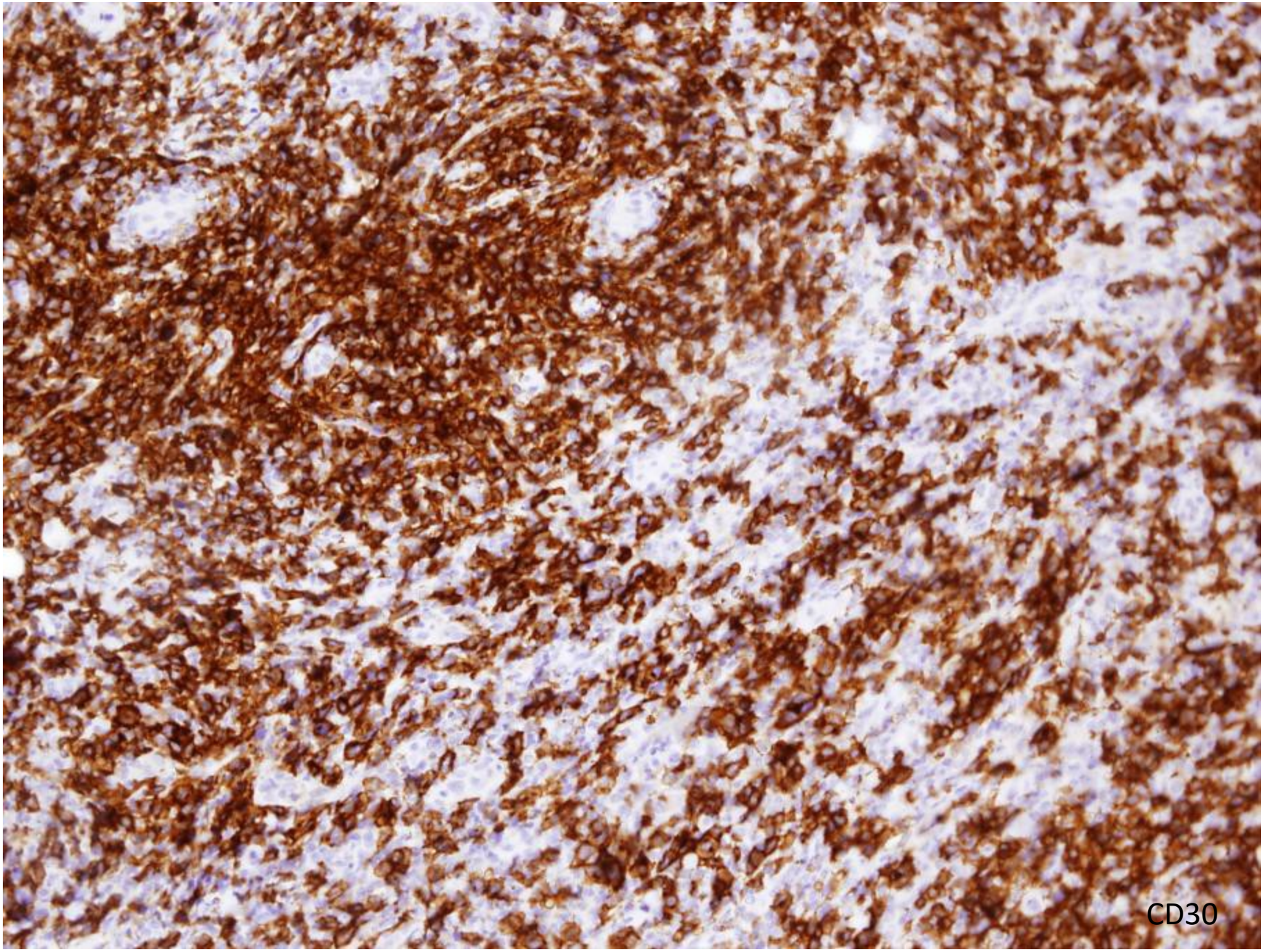
- Female, 65 years
- Oral cavity lesion







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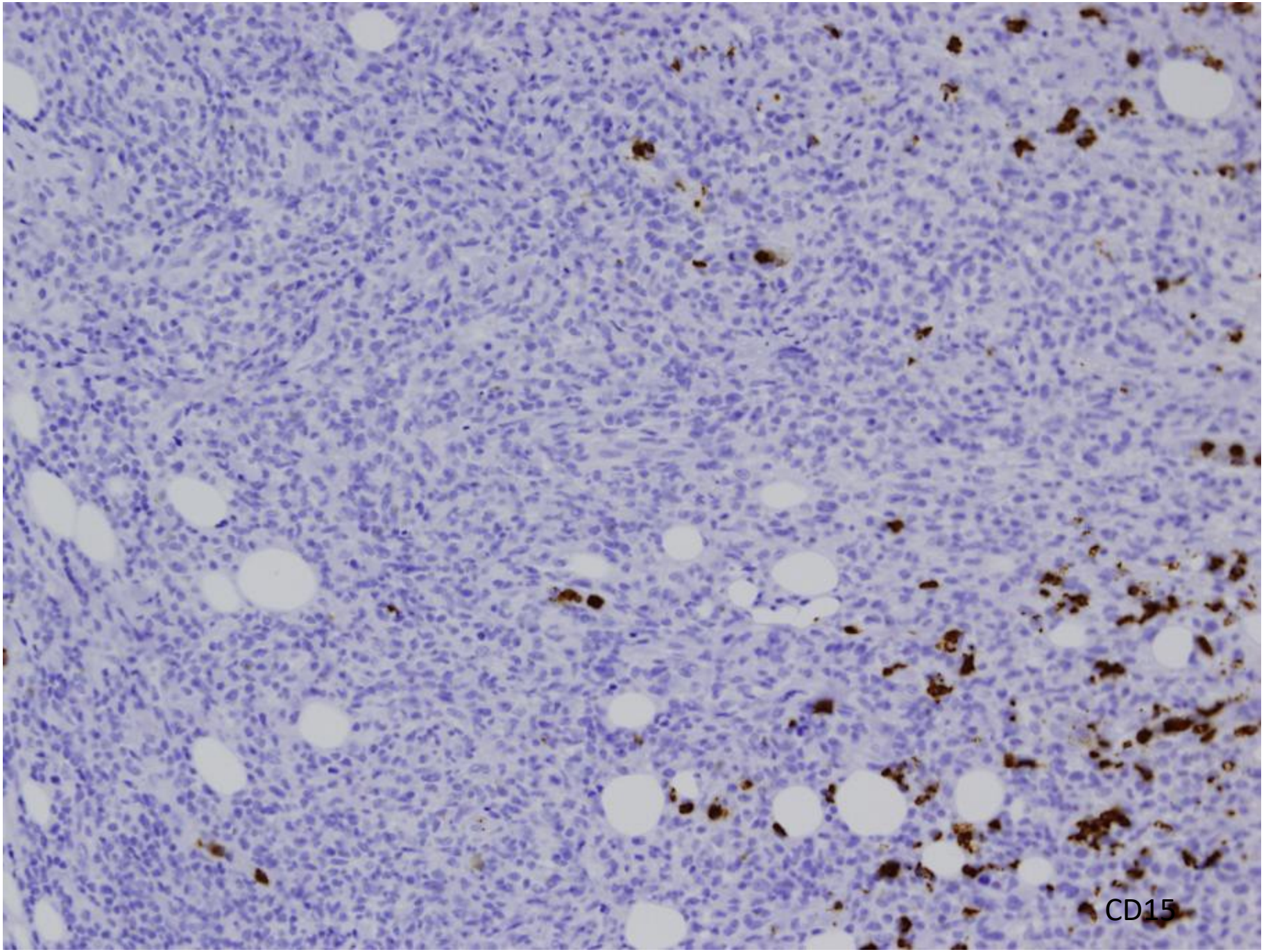
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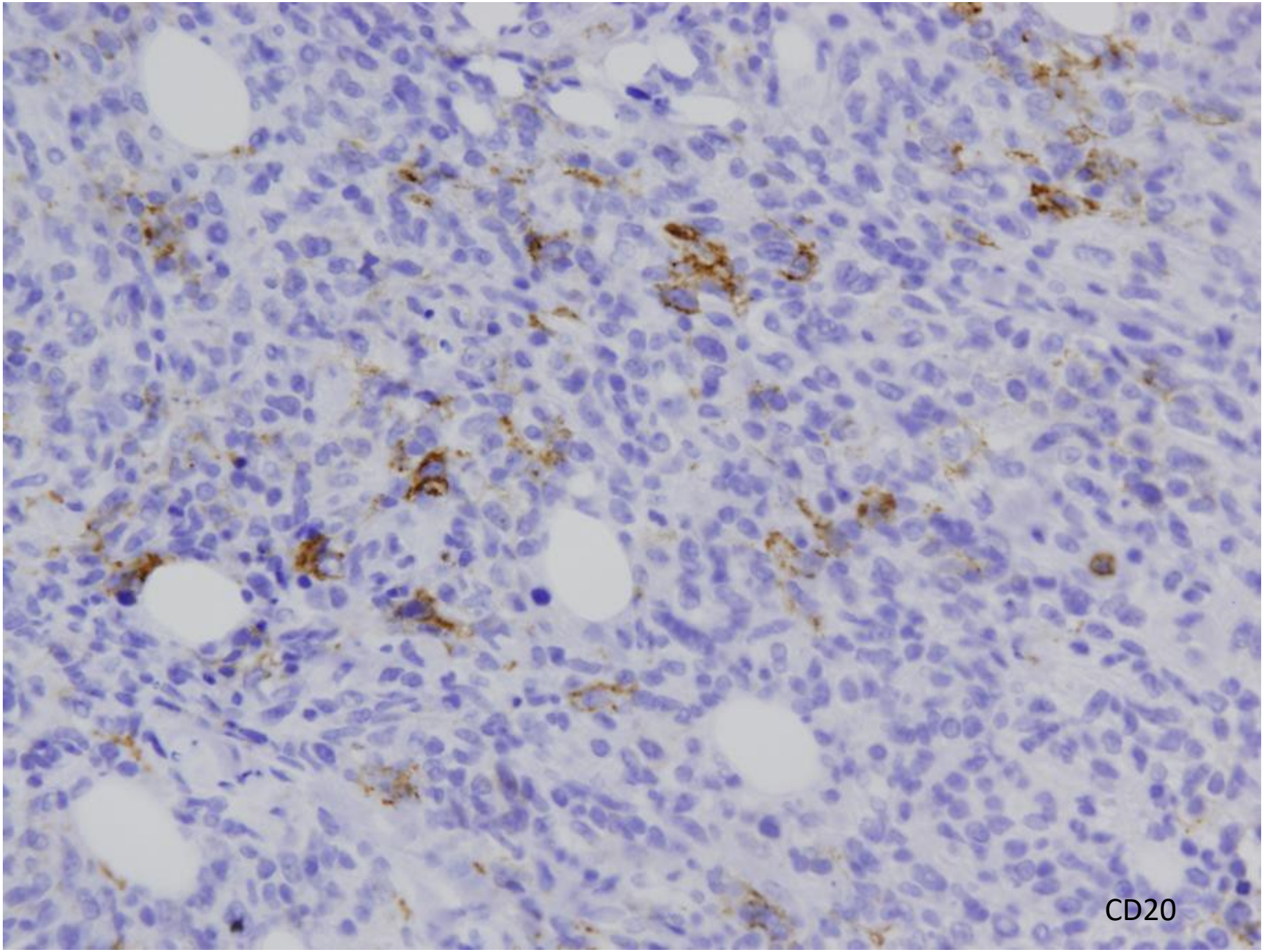
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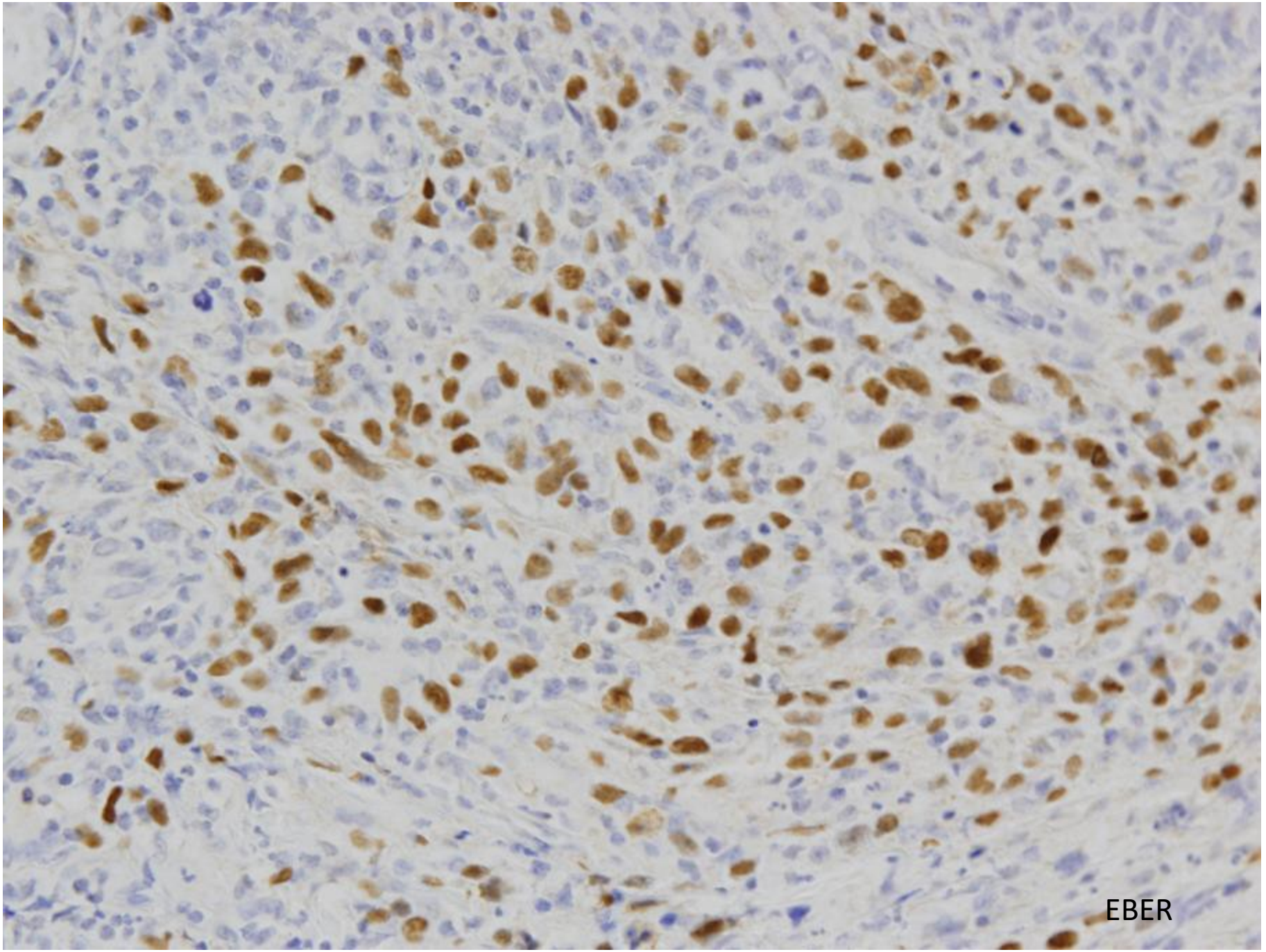
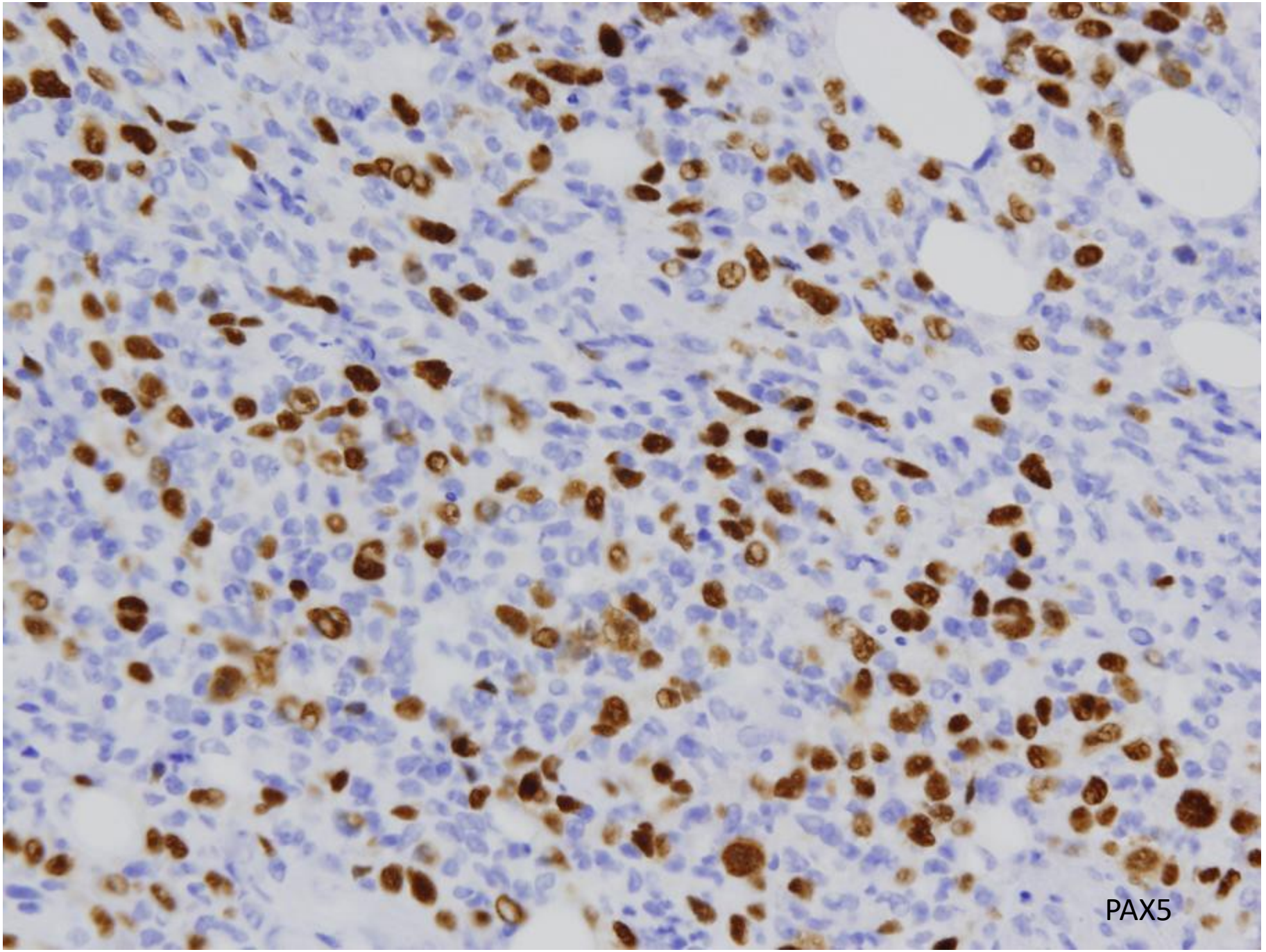

EBER


PAX5

EBV-positive mucocutaneous ulcer (EBV+ MUC)

ORIGINAL

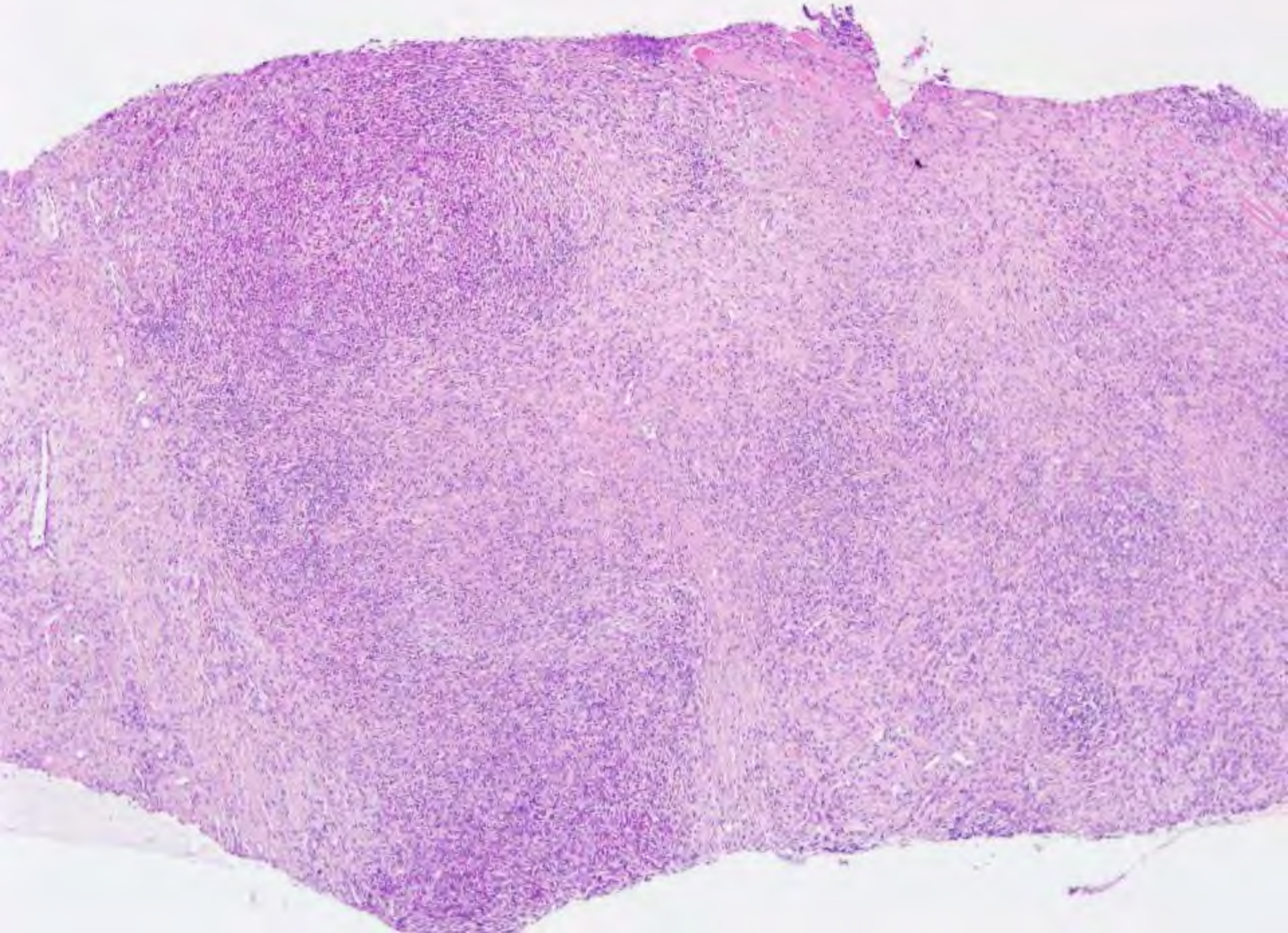
EBV Positive Mucocutaneous
Associated With Various Sou

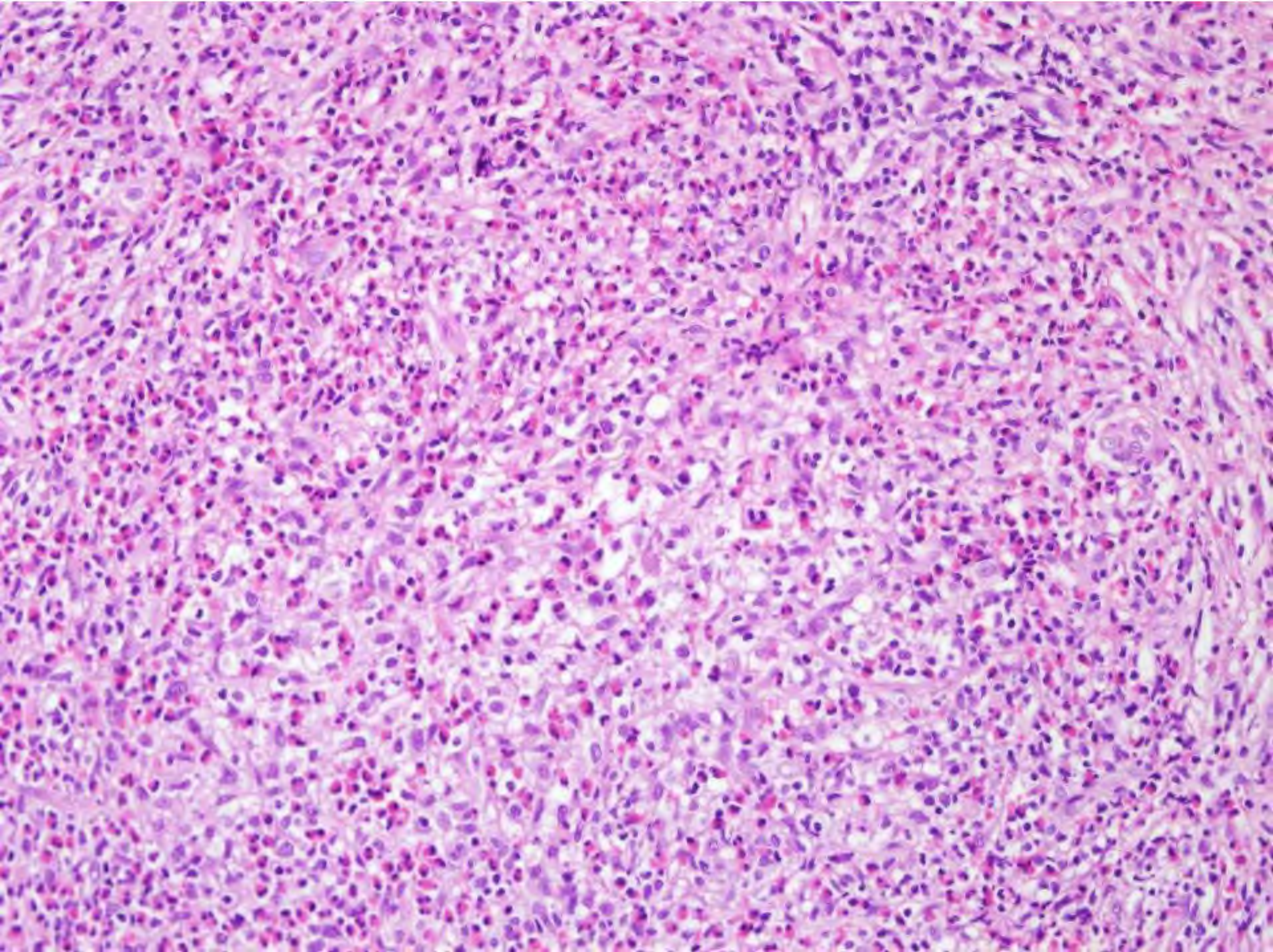
Stefan D. Dojcinov, MD, FRCPat
Mark Raffeld, MD,† Stefania Pittaluga,

Abstract: We describe a series of Epstein Barr virus (EBV)-positive circumscribed, ulcerative lesions associated with various types of immunosuppression (IS). The study group (26 patients) comprised 10 males and 16 females, median age 77 years (range 42 to 101). IS in 9 cases included azathioprine (AZA), methotrexate (MTX) or cyclosporin-A (CyA). Seventeen patients had age-related immunosenescence. Patients presented with isolated sharply circumscribed ulcers involving oropharyngeal mucosa (16), skin (6), and gastrointestinal tract (4). Lesions were histologically characterized by a polymorphous infiltrate and atypical large B-cell blasts often with Hodgkin/Reed-Sternberg (HRS) cell-like morphology. The B cells showed strong CD30 and EBER positivity, some with reduced CD20 expression, in a background of abundant T cells. CD15 was positive in 43% of cases (10/23). The pathologic features were identical regardless of the anatomic site or cause of IS. Polymerase chain reaction revealed 39% (7/18) clonal Ig gene rearrangements with 38% (6/16) and 31% (5/16) clonal and restricted T-cell patterns, respectively. Twenty-five percent of patients (5/20) received standard chemotherapy and/or radiotherapy. Forty-five percent (9/20) regressed spontaneously with no treatment and 15% (3/20) were characterized by a relapsing and remitting course. All of the iatrogenic lesions (6/6) with available follow-up responded to reduction of IS. All patients achieved complete remission with no disease-associated deaths over a median follow-up period of 22 months (range 3 to 72). We propose EBV-positive mucocutaneous ulcer as a newly recognized clinicopathologic entity with Hodgkin-like features and a self-limited, indolent course, generally responding well to conservative management. Association with various forms of IS implies a common pathogenetic mechanism. The localized nature of the disease may be owing to a minimal and localized lapse in immunosurveillance over EBV.

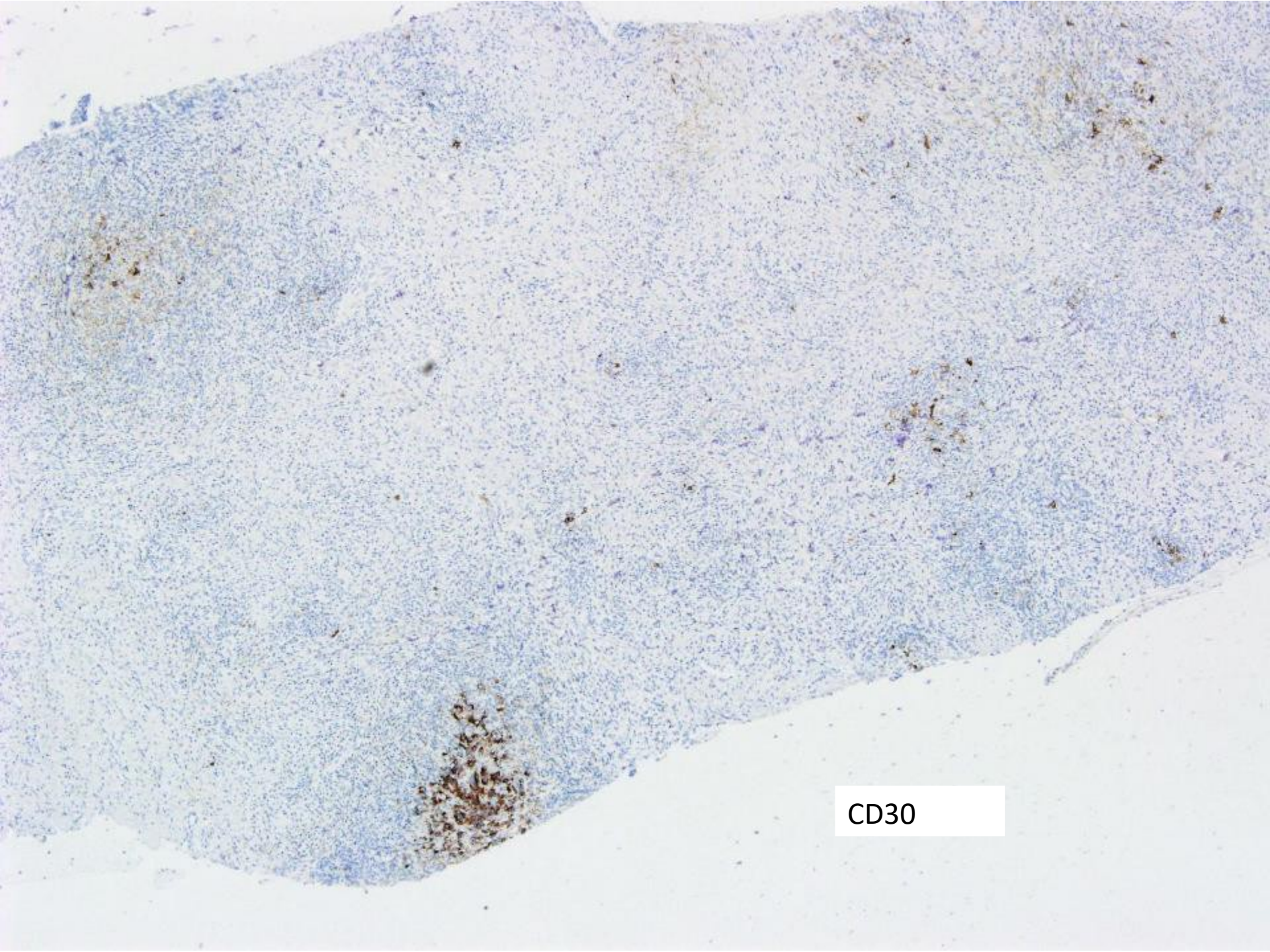
Case 7

- 73 yrs old female, renal transplant 2 yrs. ago
- Bucal ulcer +
- cervical lymphadenopathy






EBER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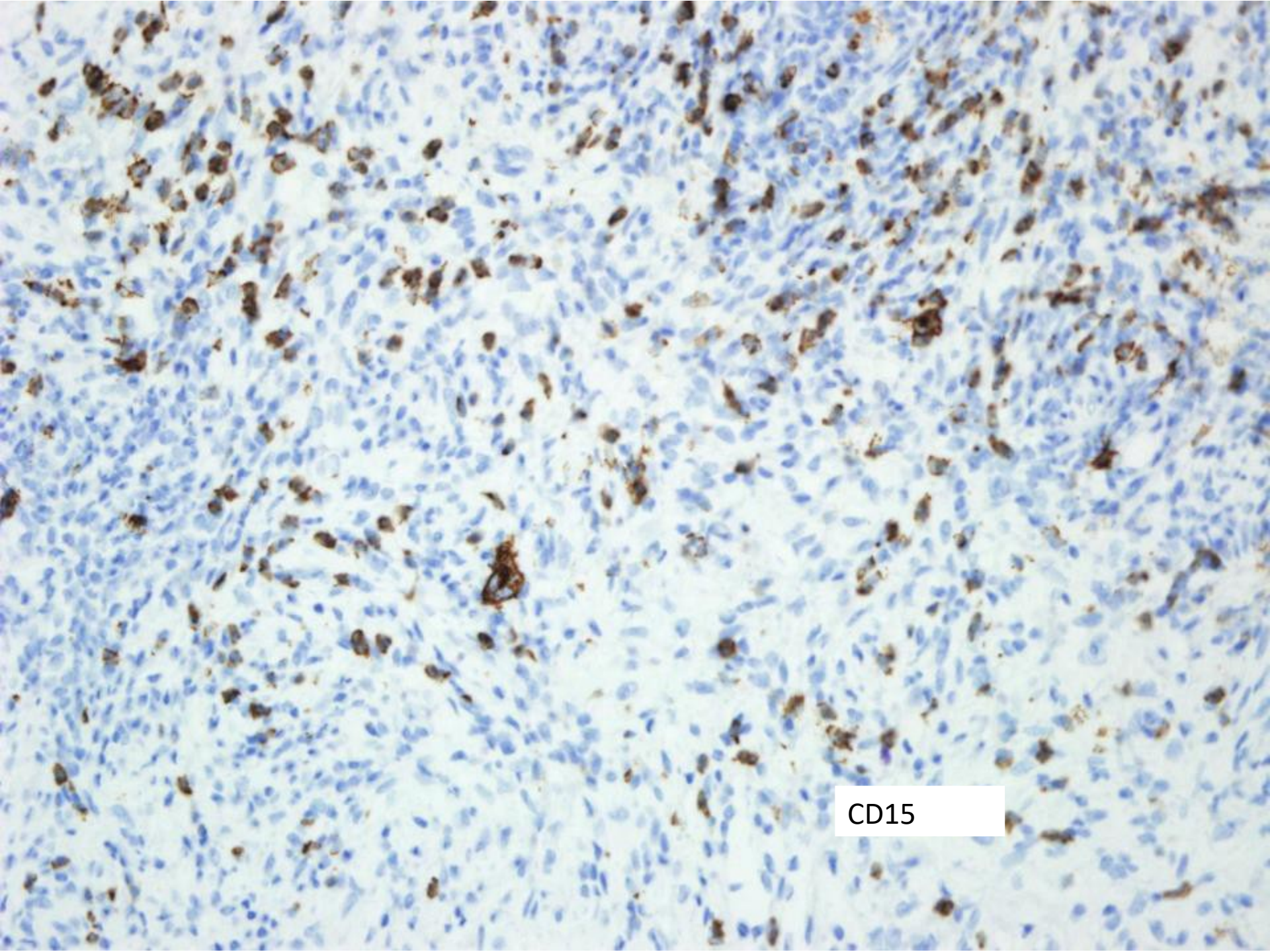
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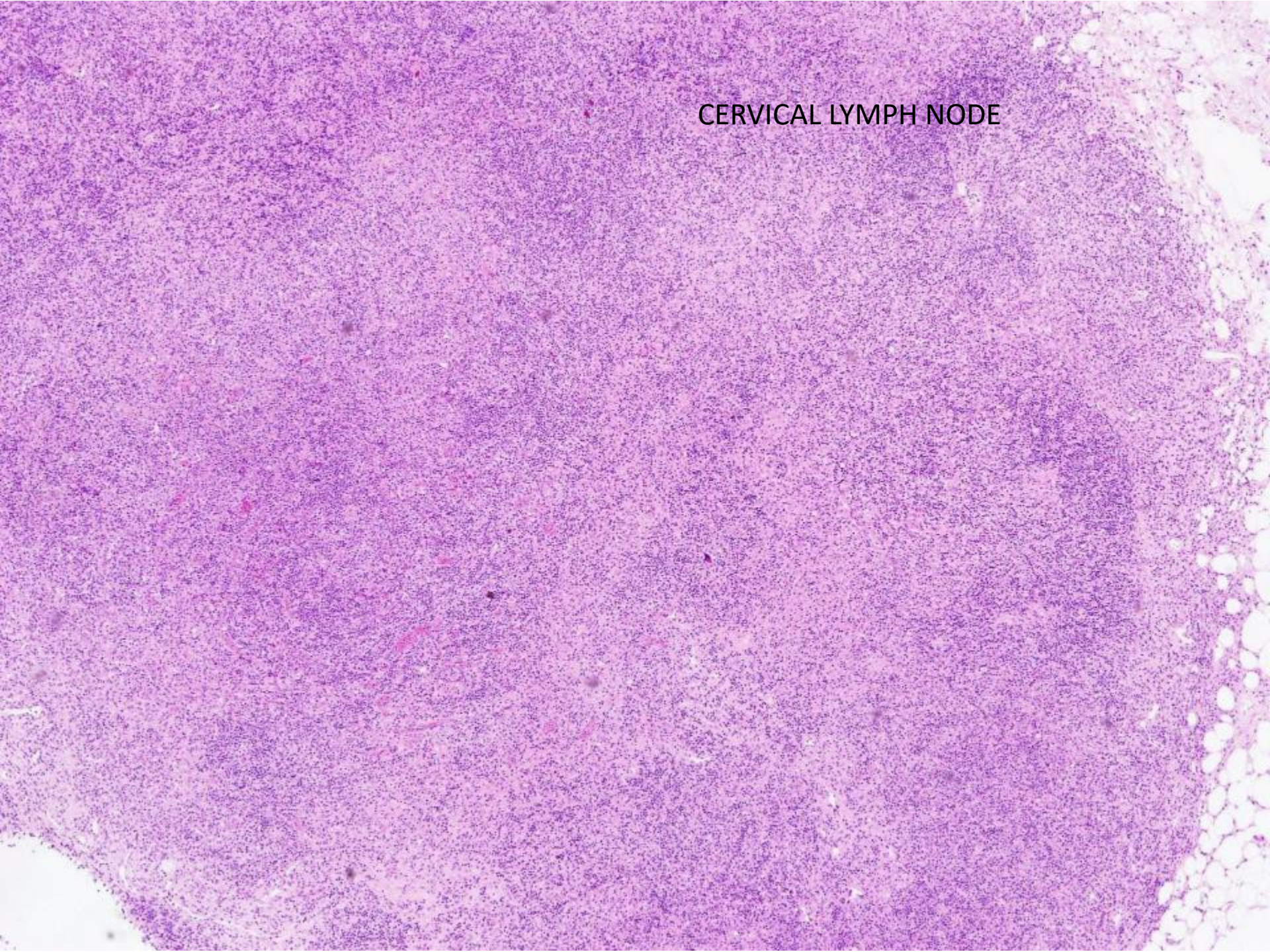
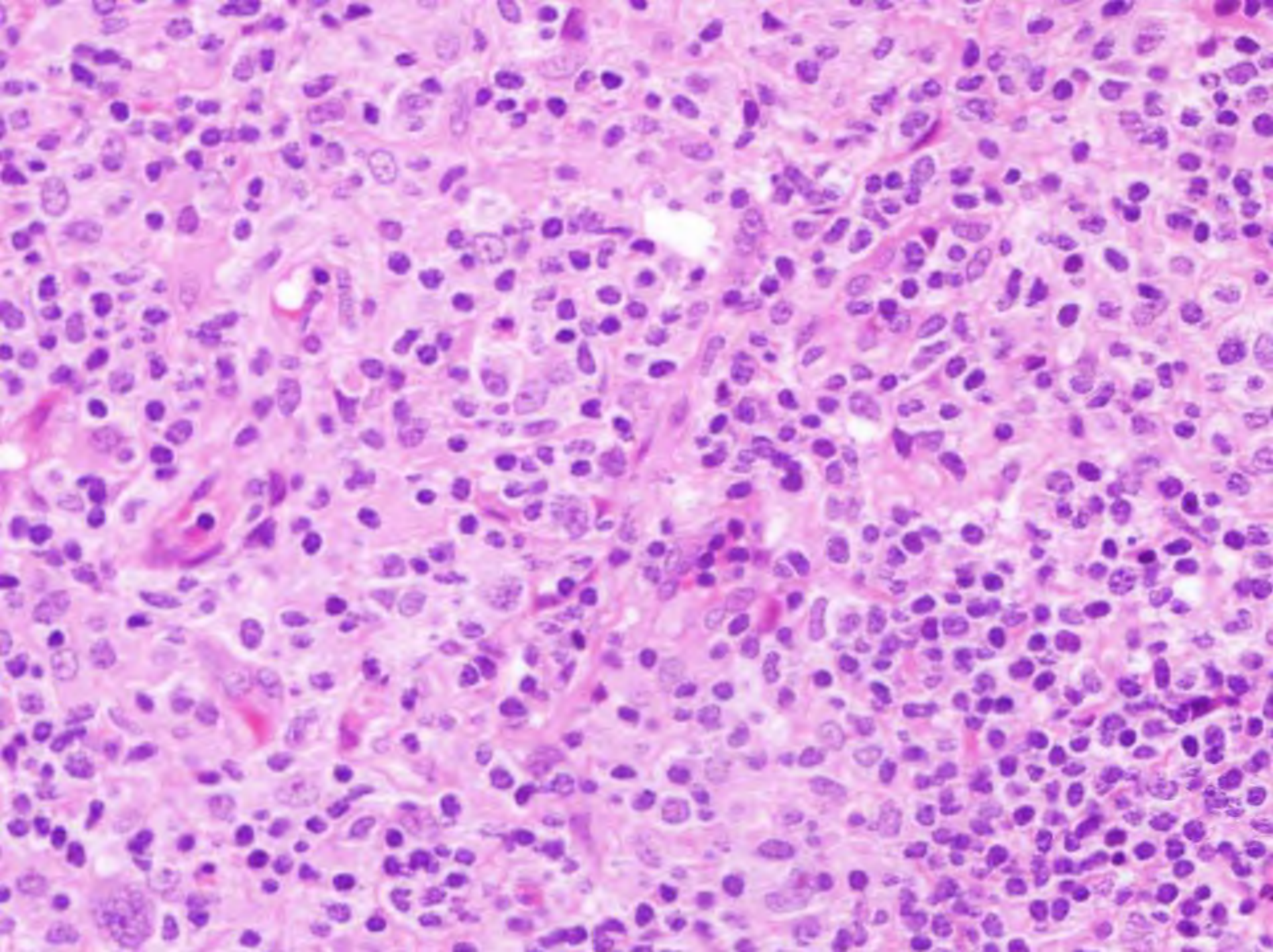
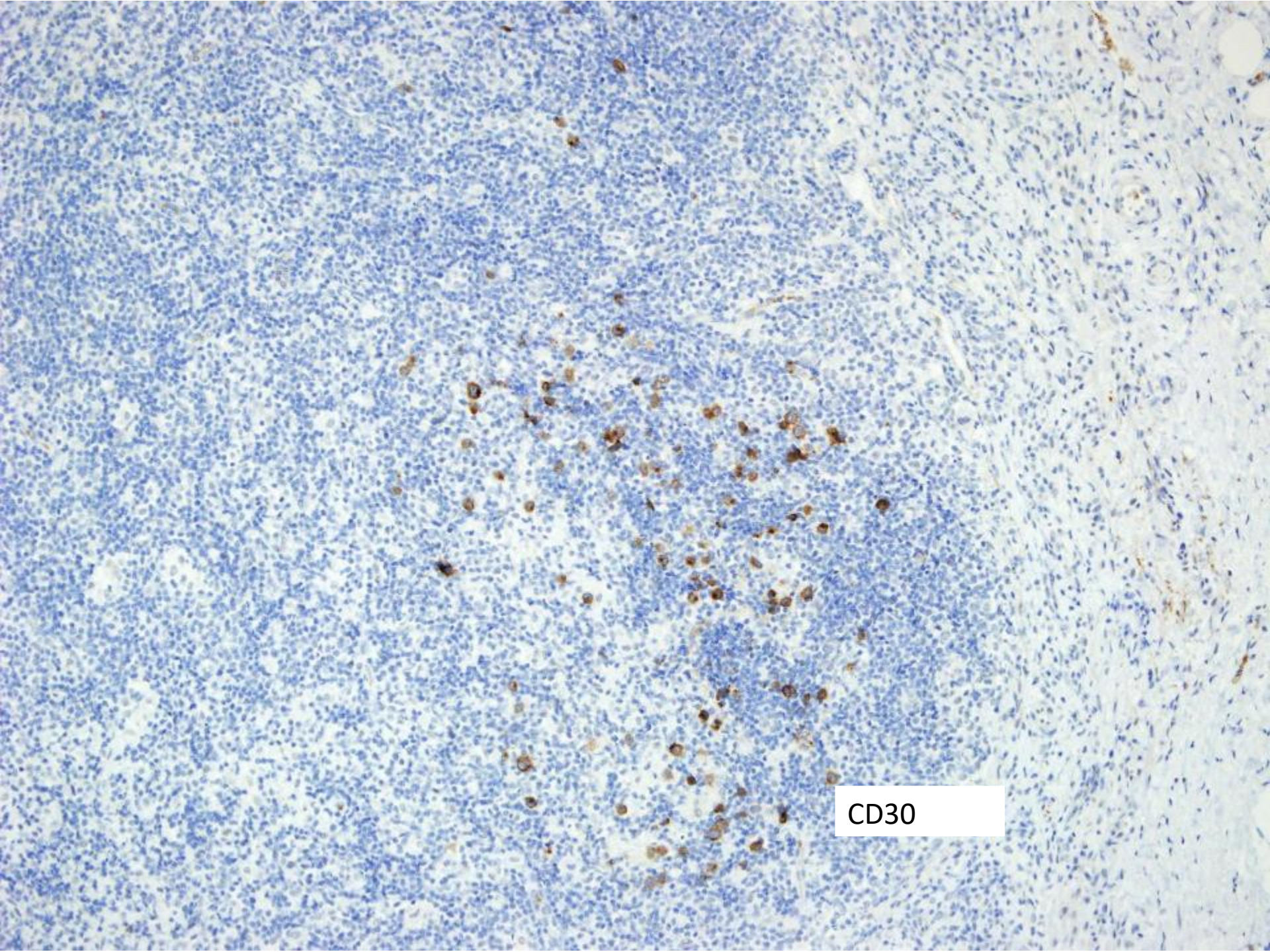

CERVICAL LYMPH NODE

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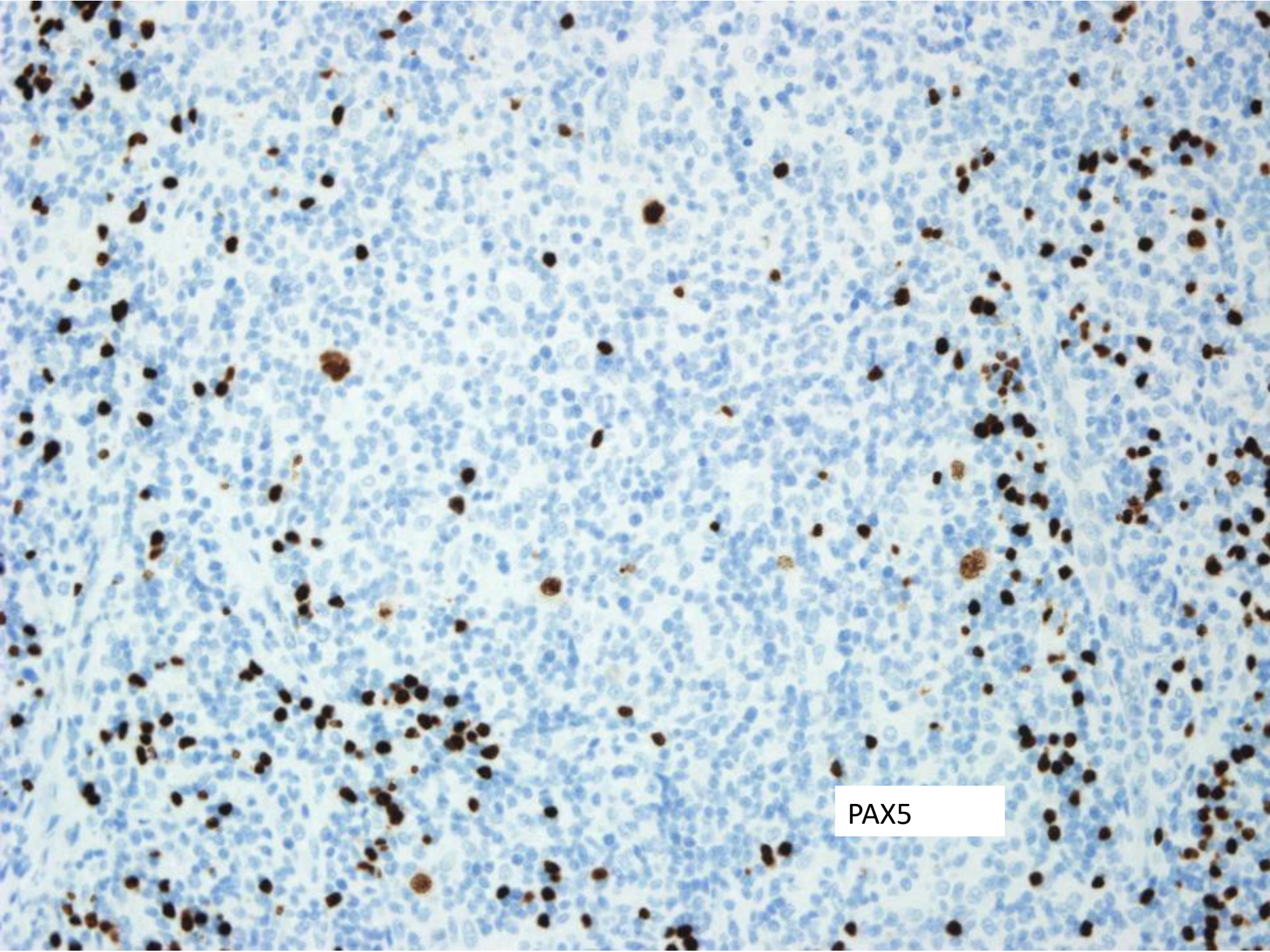
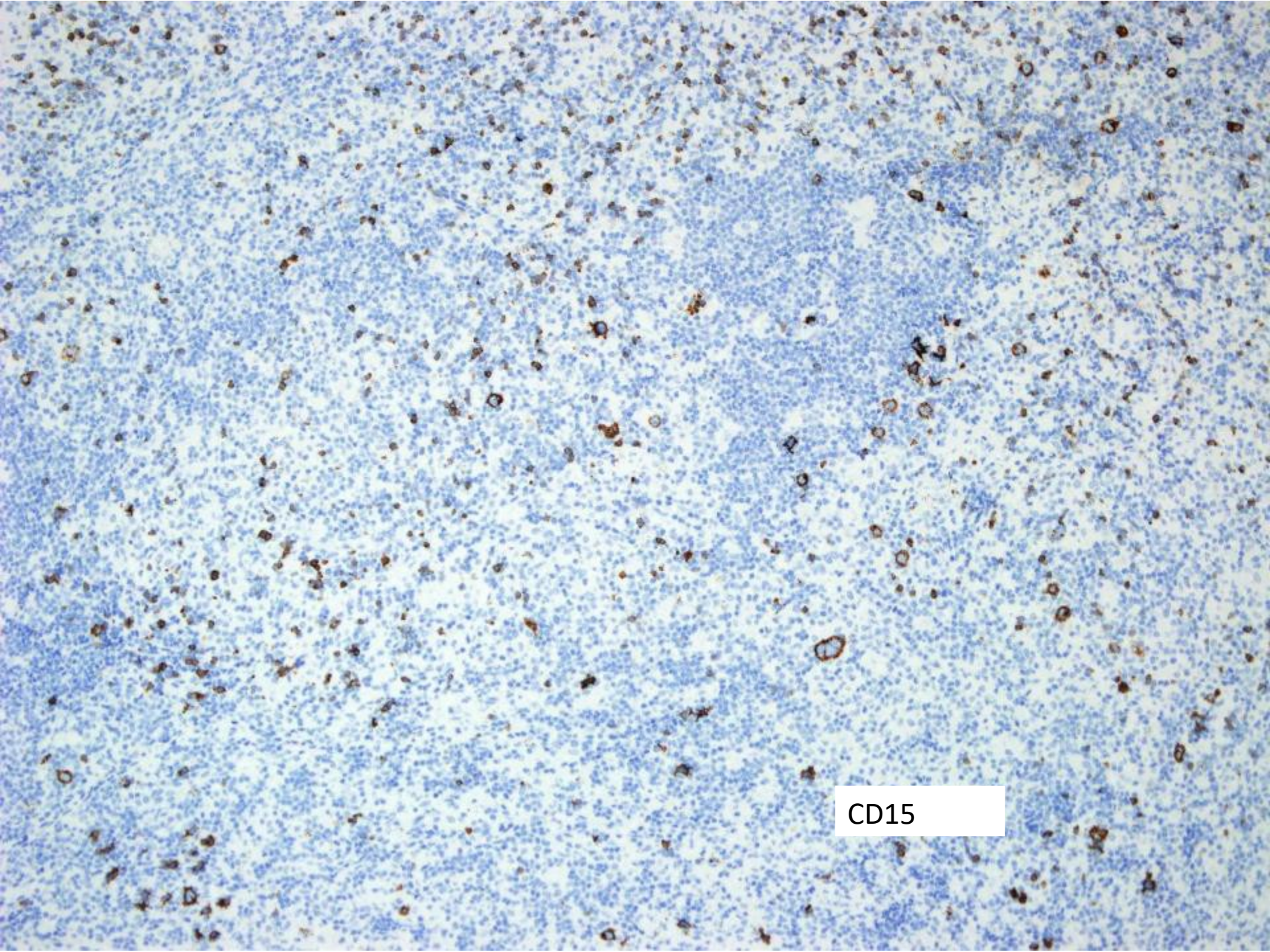

PAX5


CD15

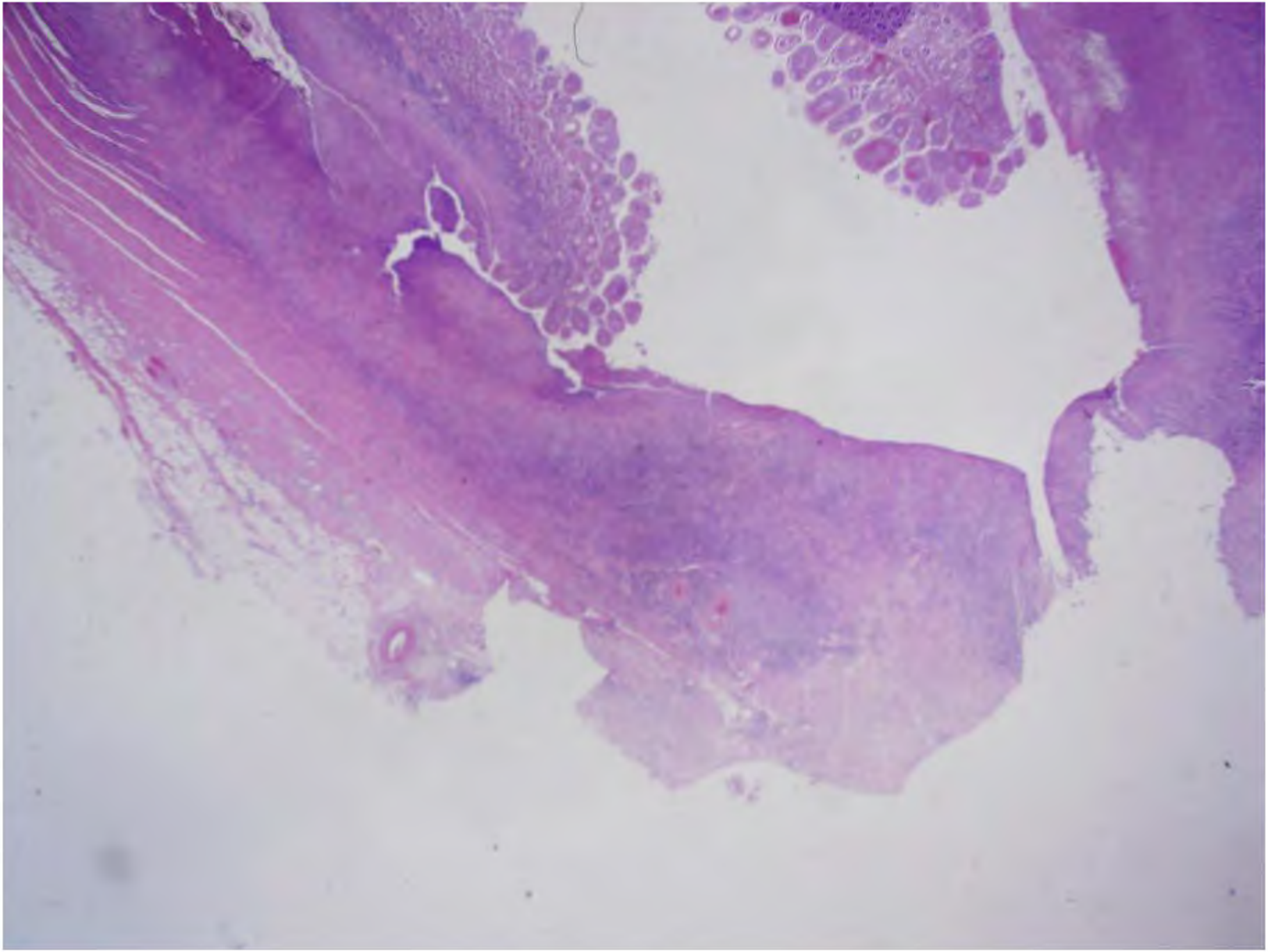
EBV+ MUCOCUTANEOUS ULCER

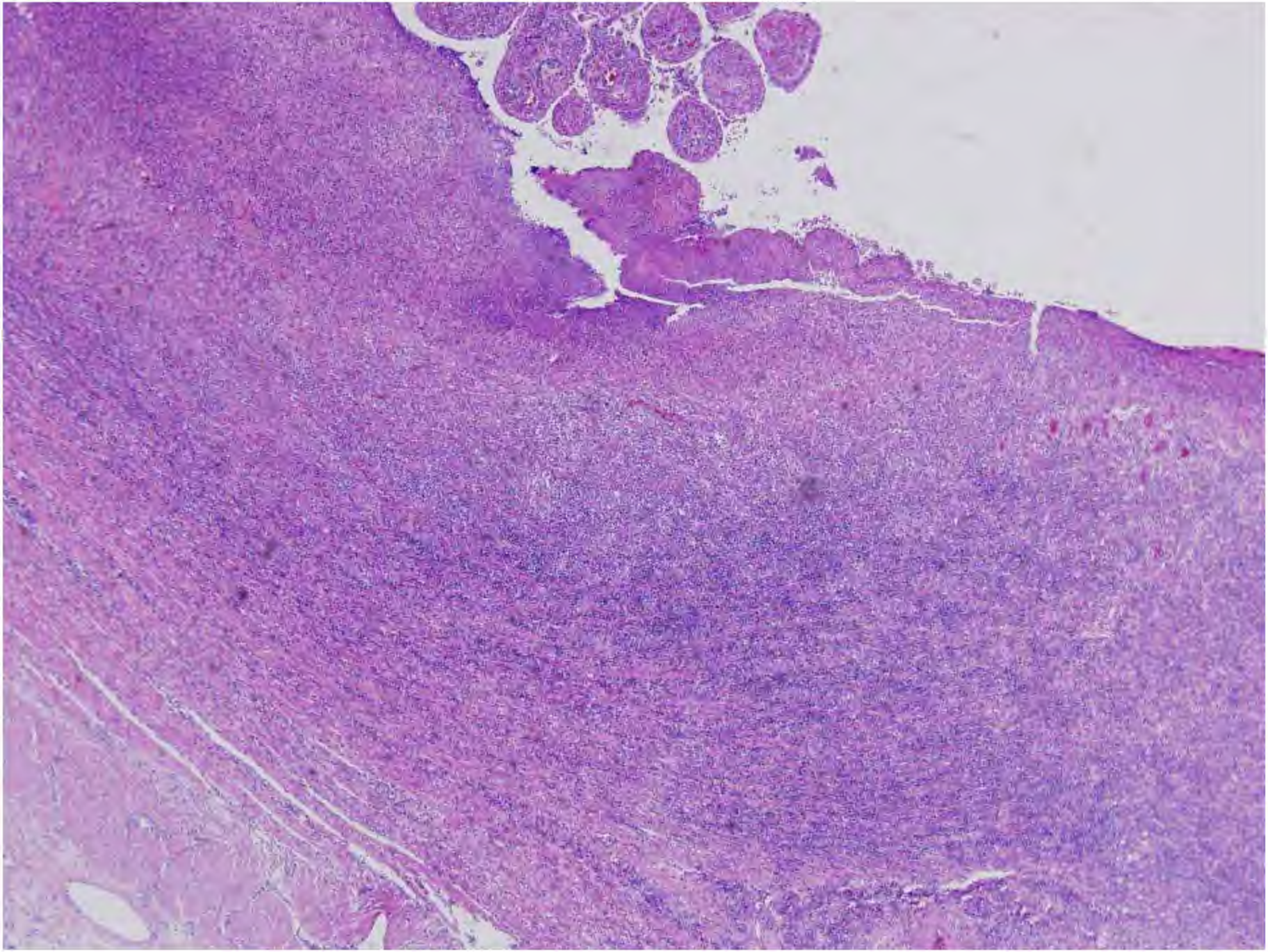
Part of the spectrum of the EBV+ lymphoproliferative disorders associated with immunosuppression

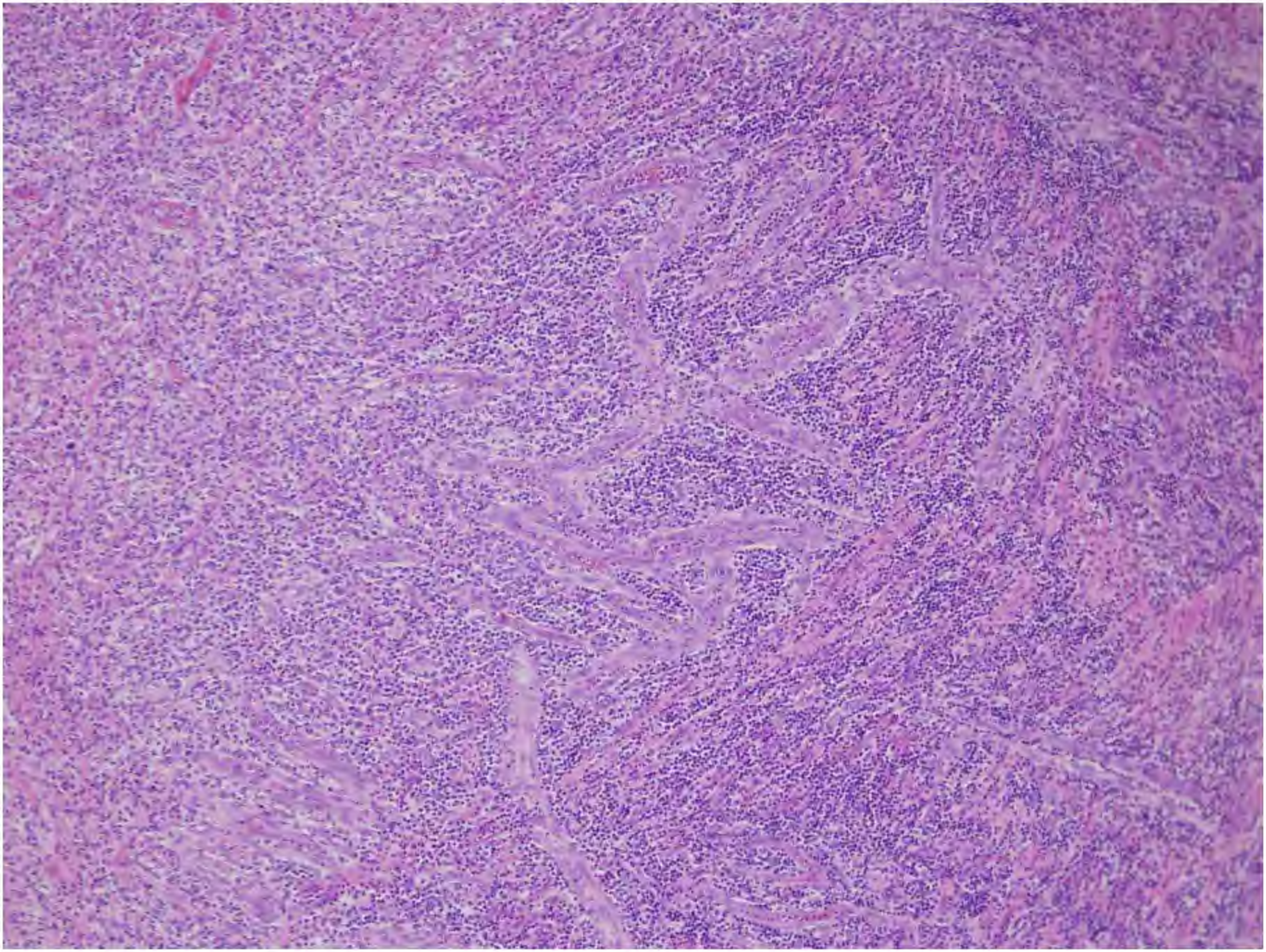
EBV+ PTLD polyclonal
EBV+ PTLD monoclonal
EBV+ DLBCL

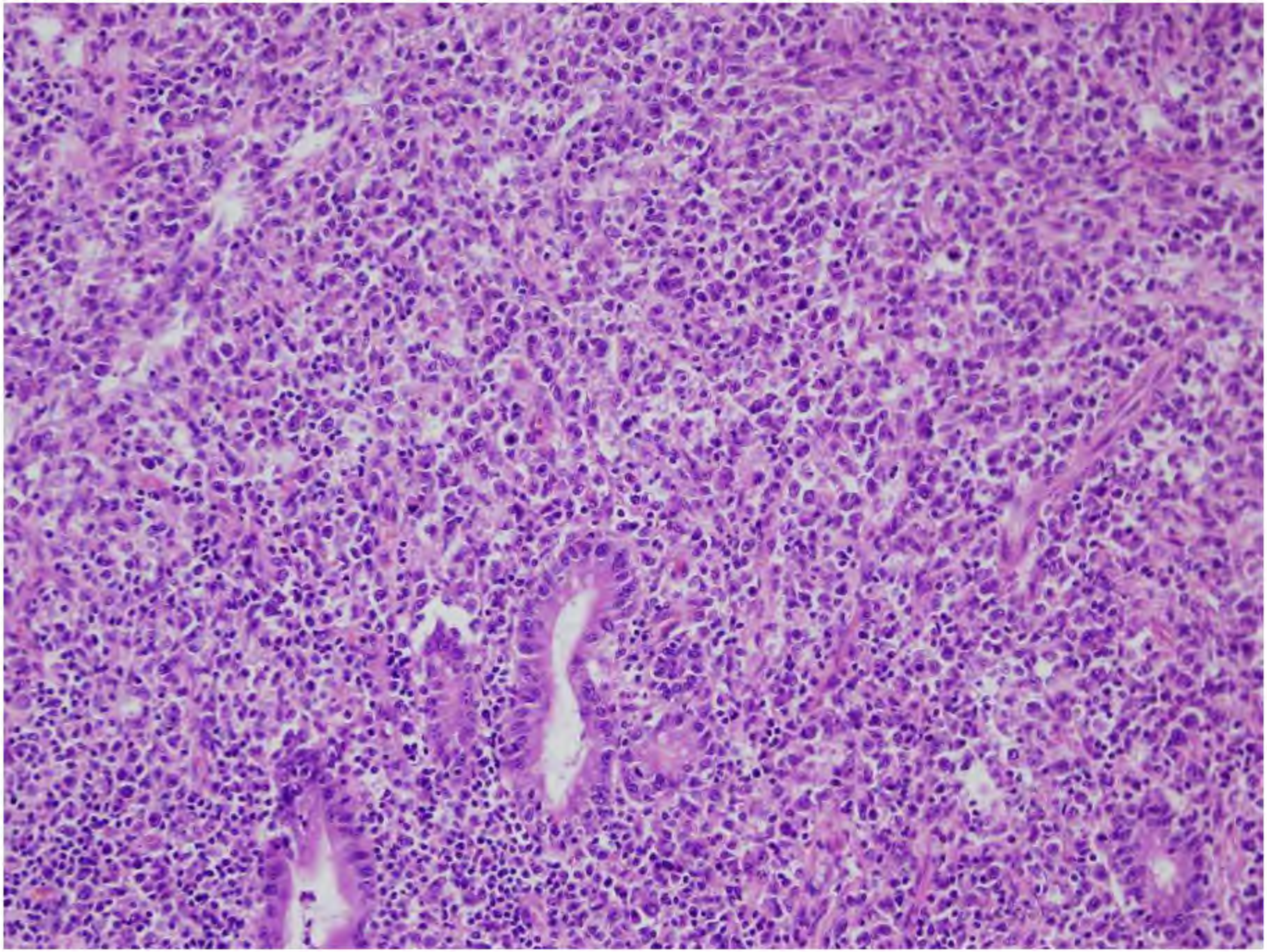
Case 8

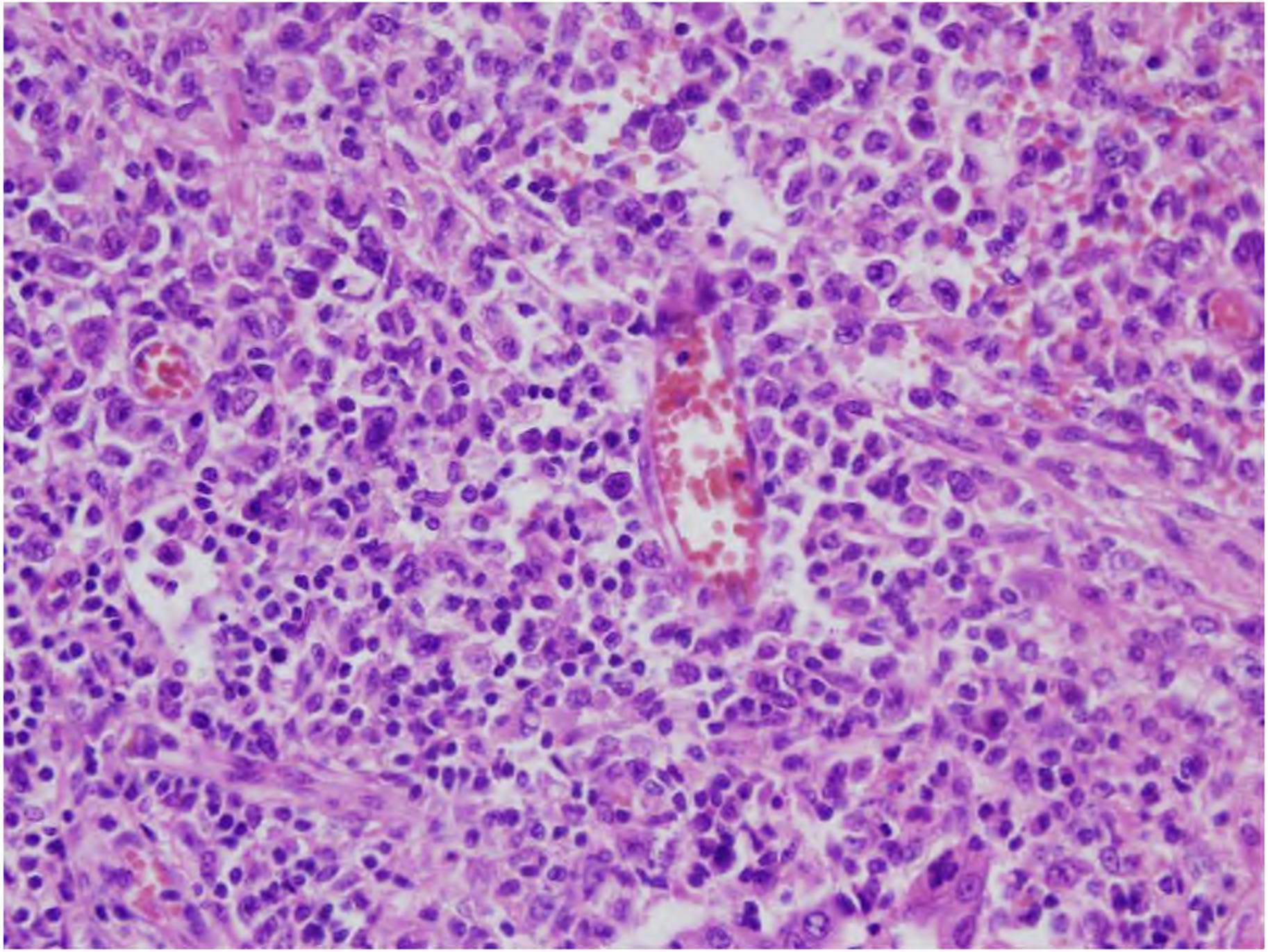
- Female 50 yrs
- Renal transplant and immunosuppression

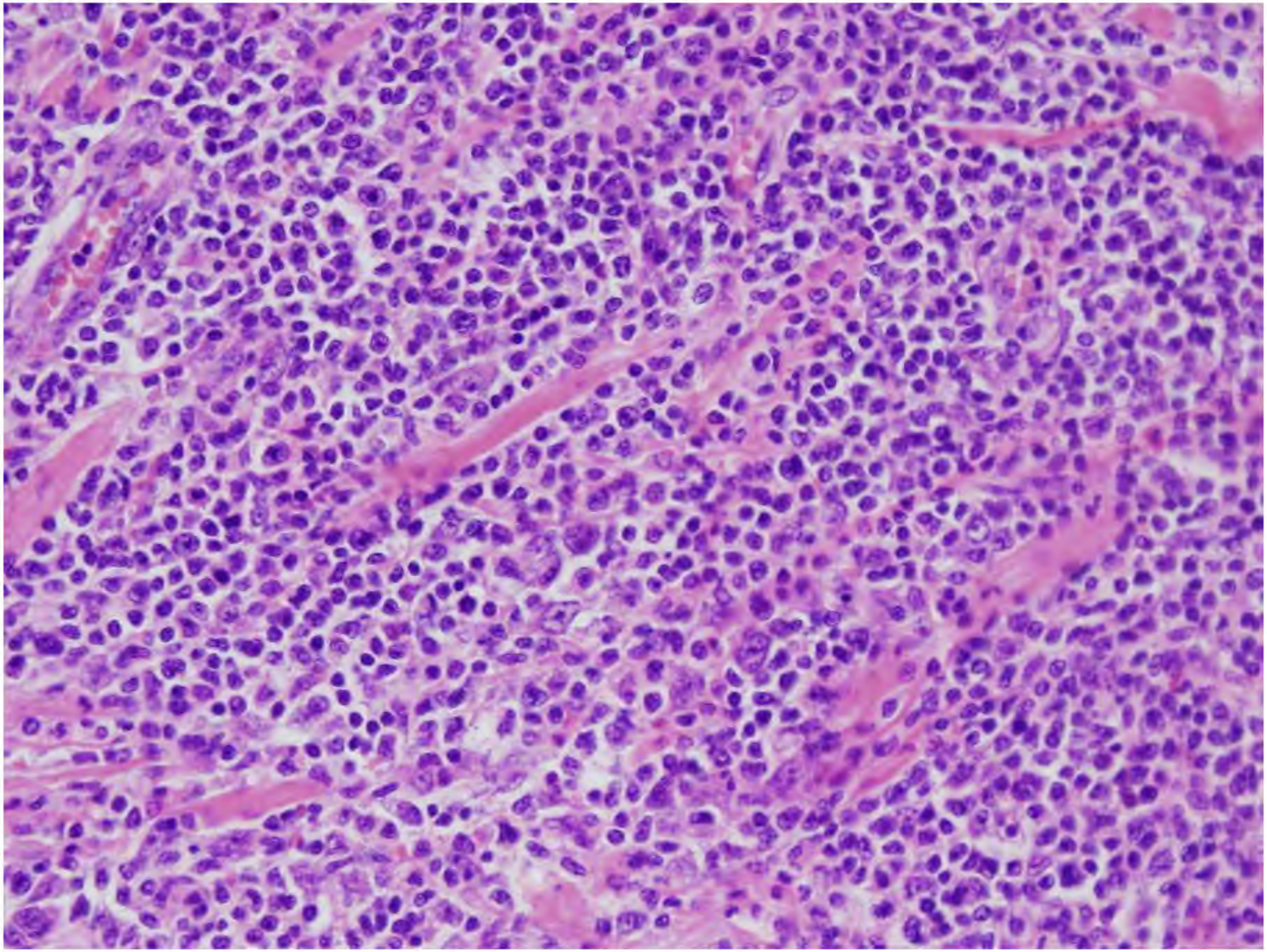


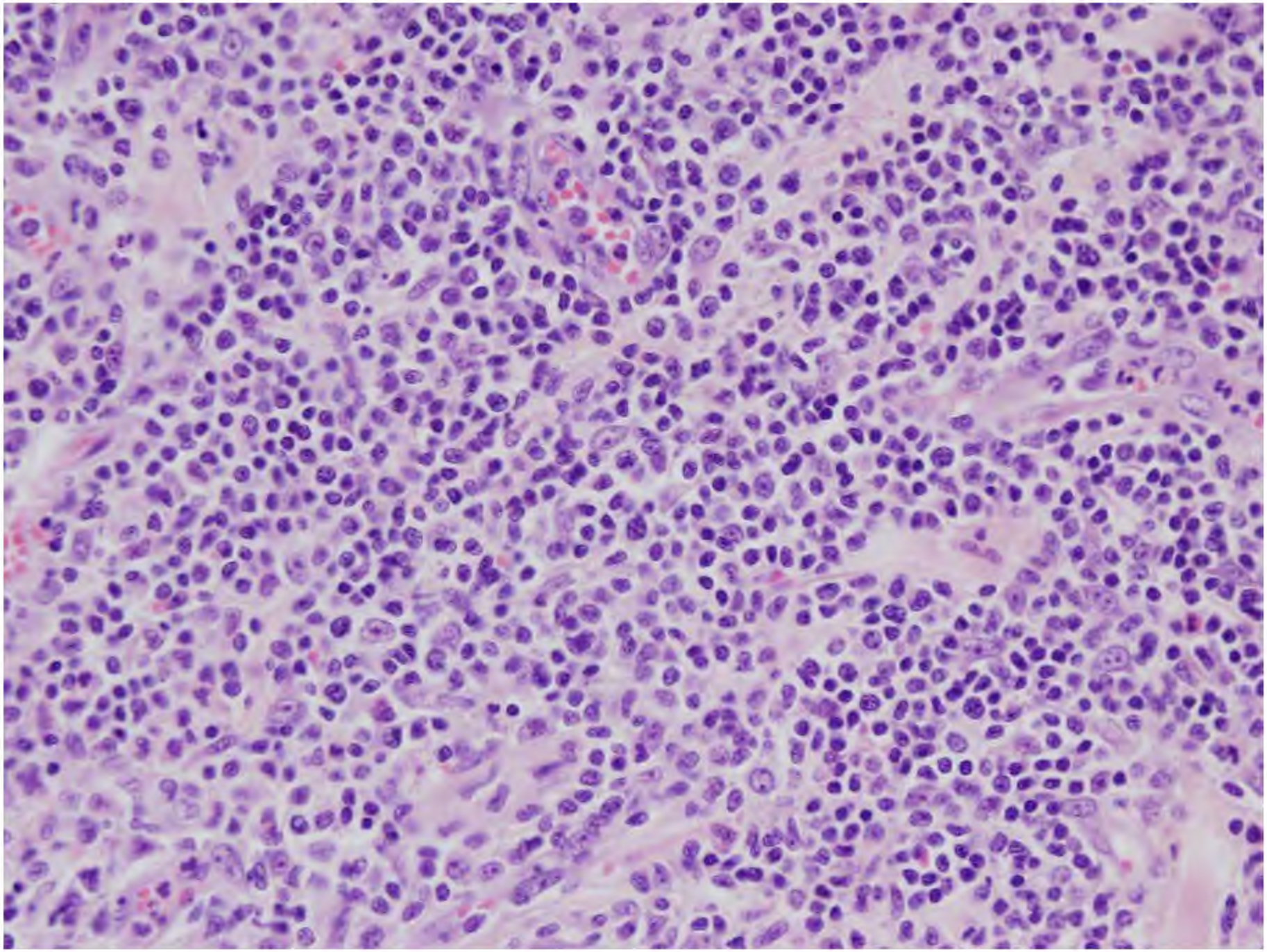


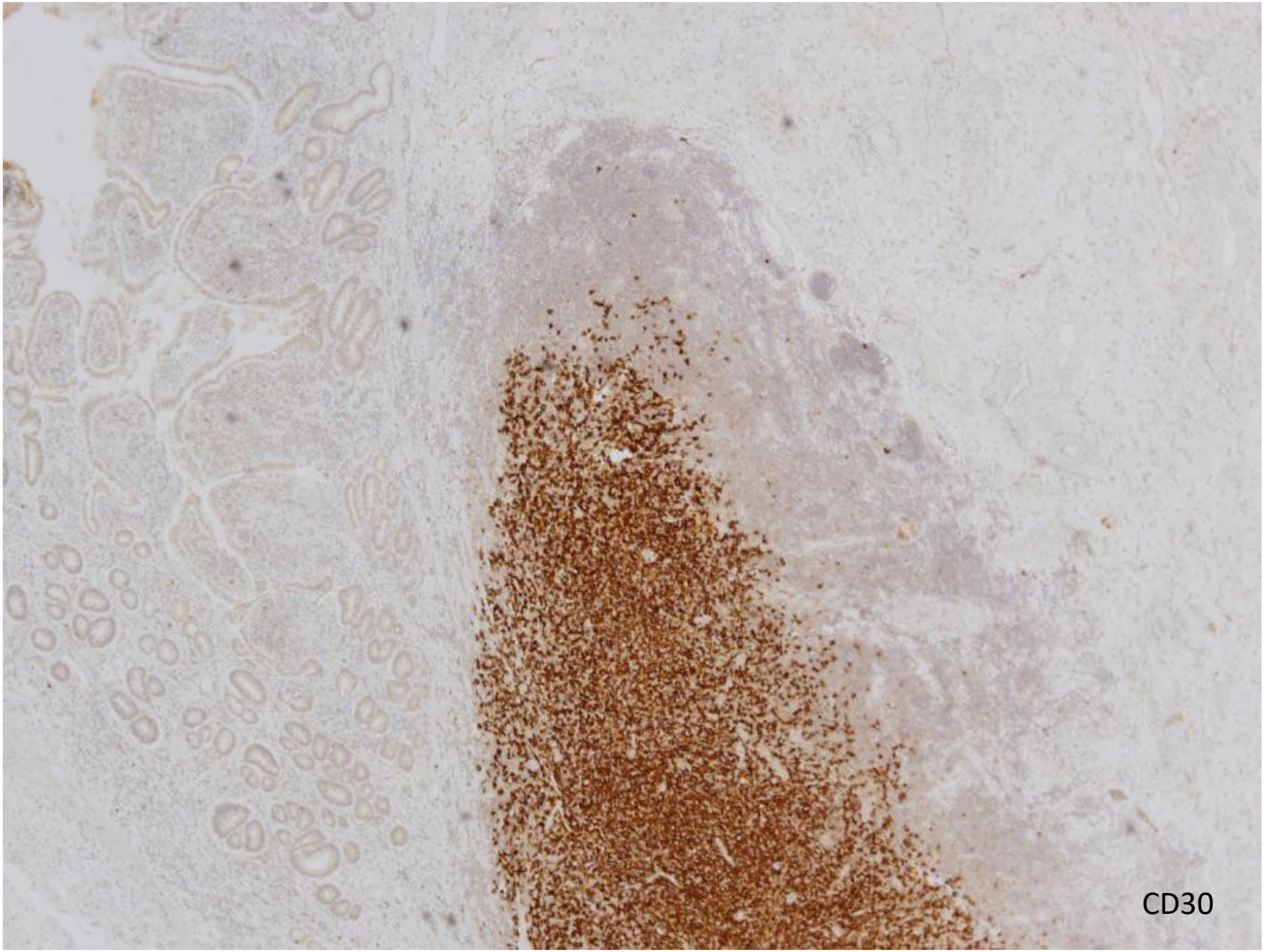


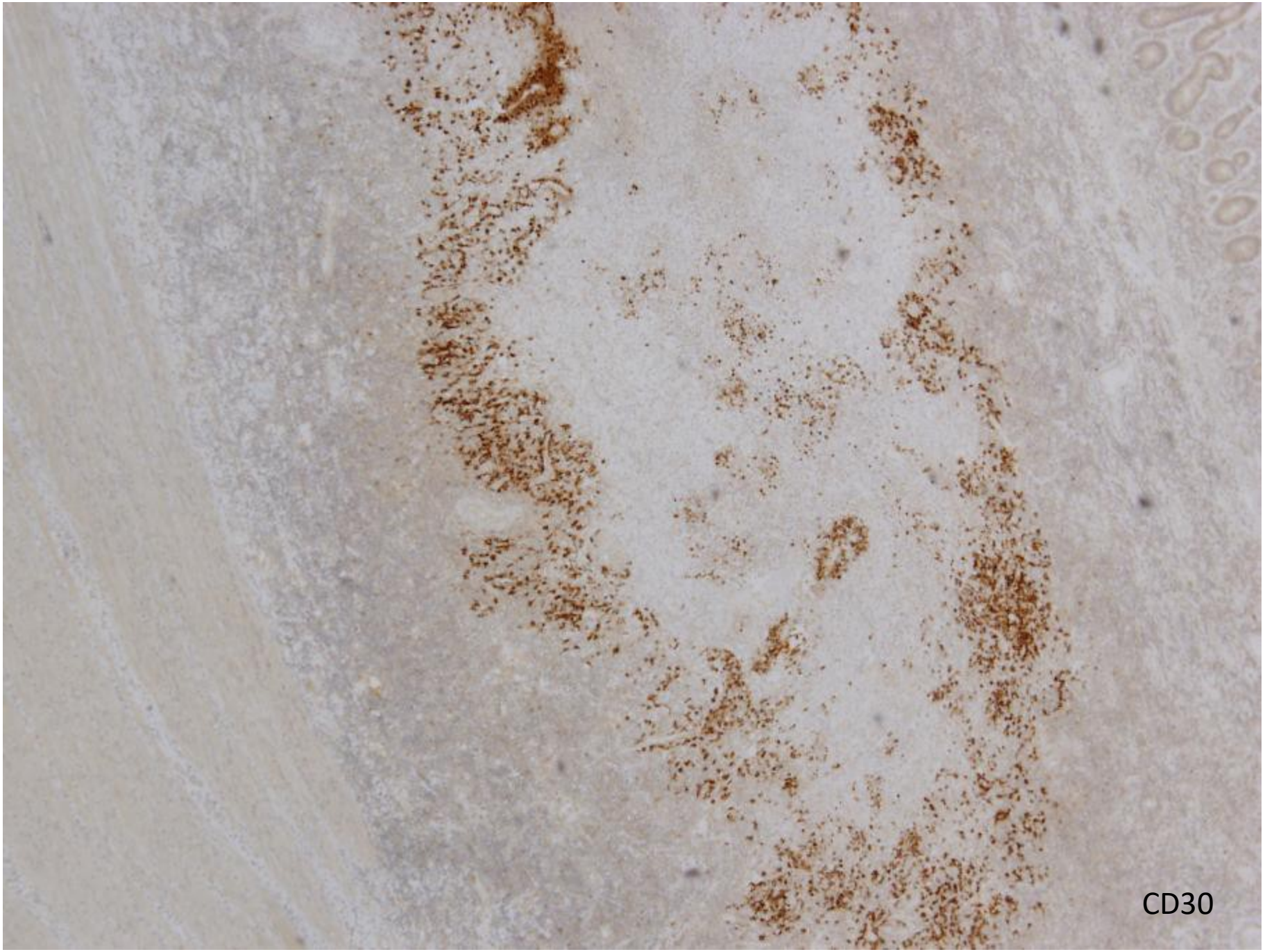









CD30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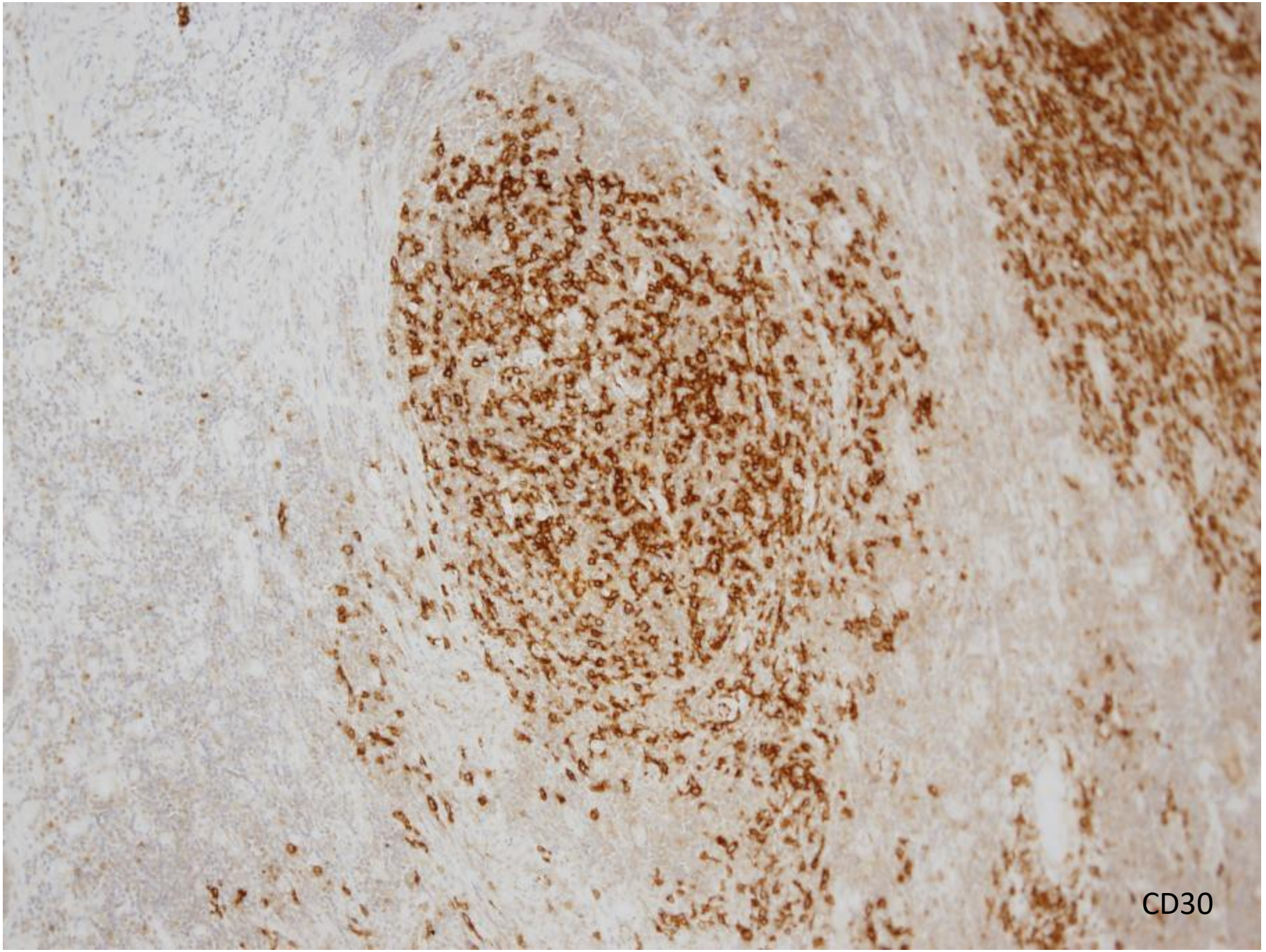
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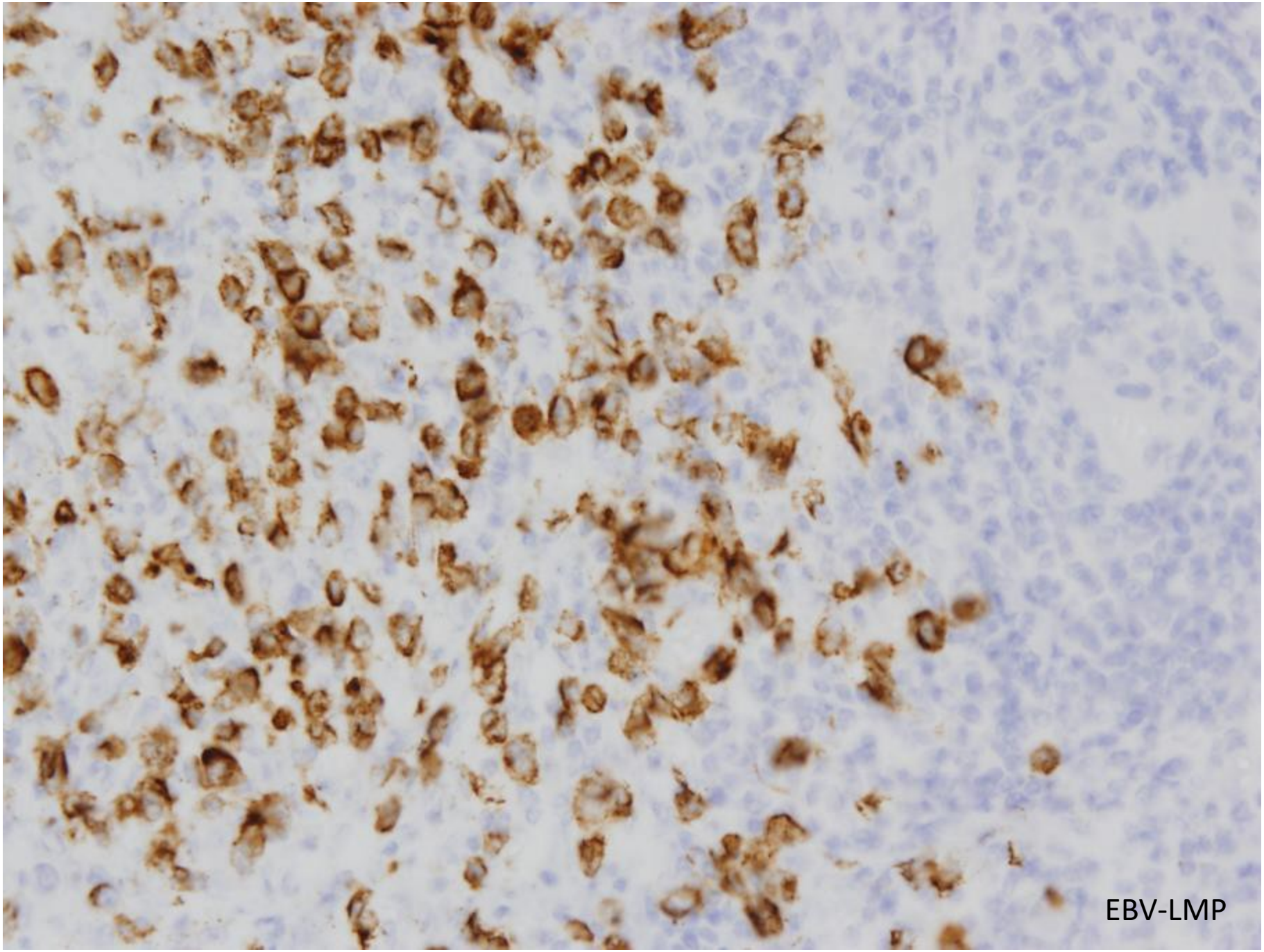
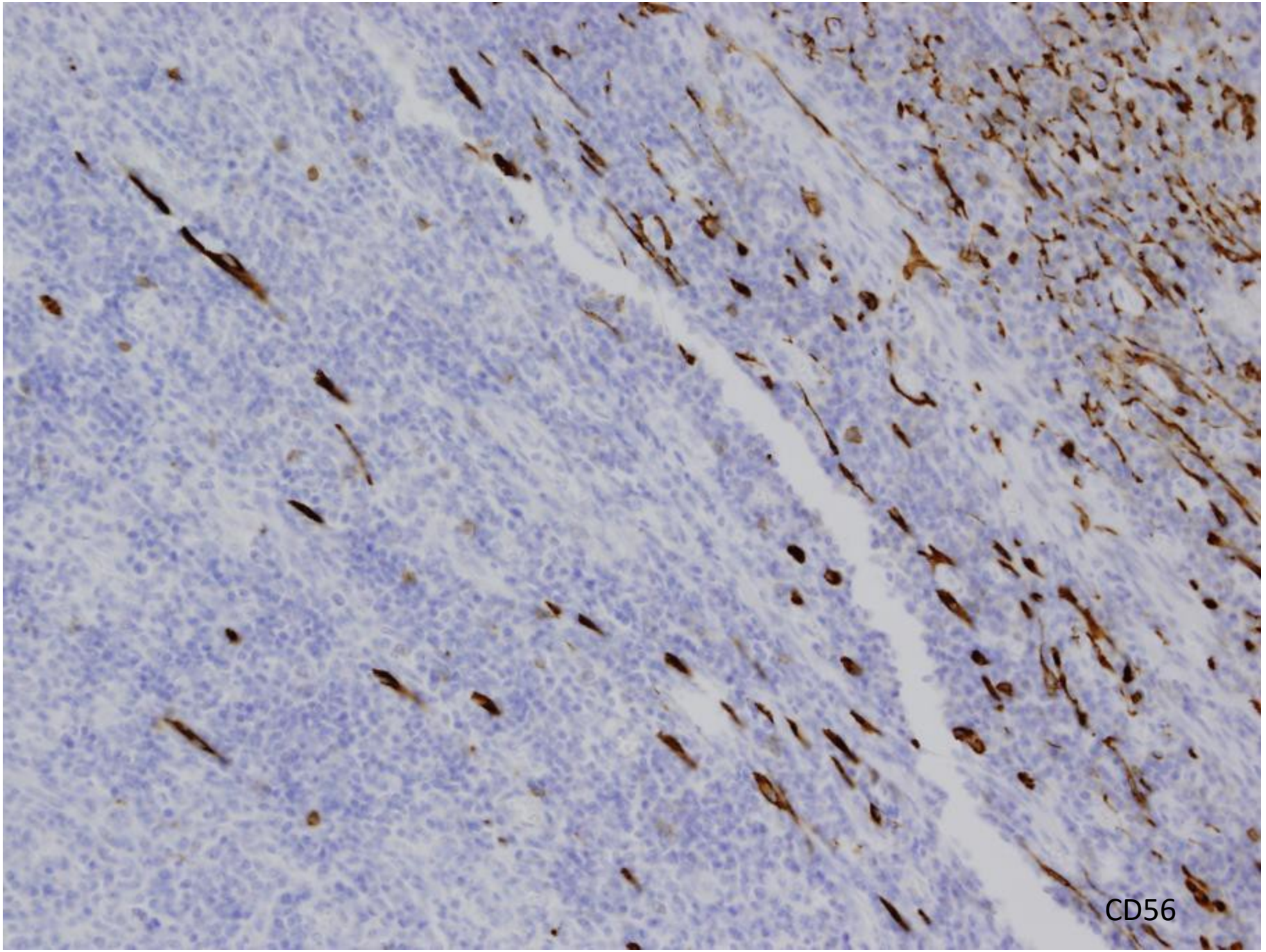
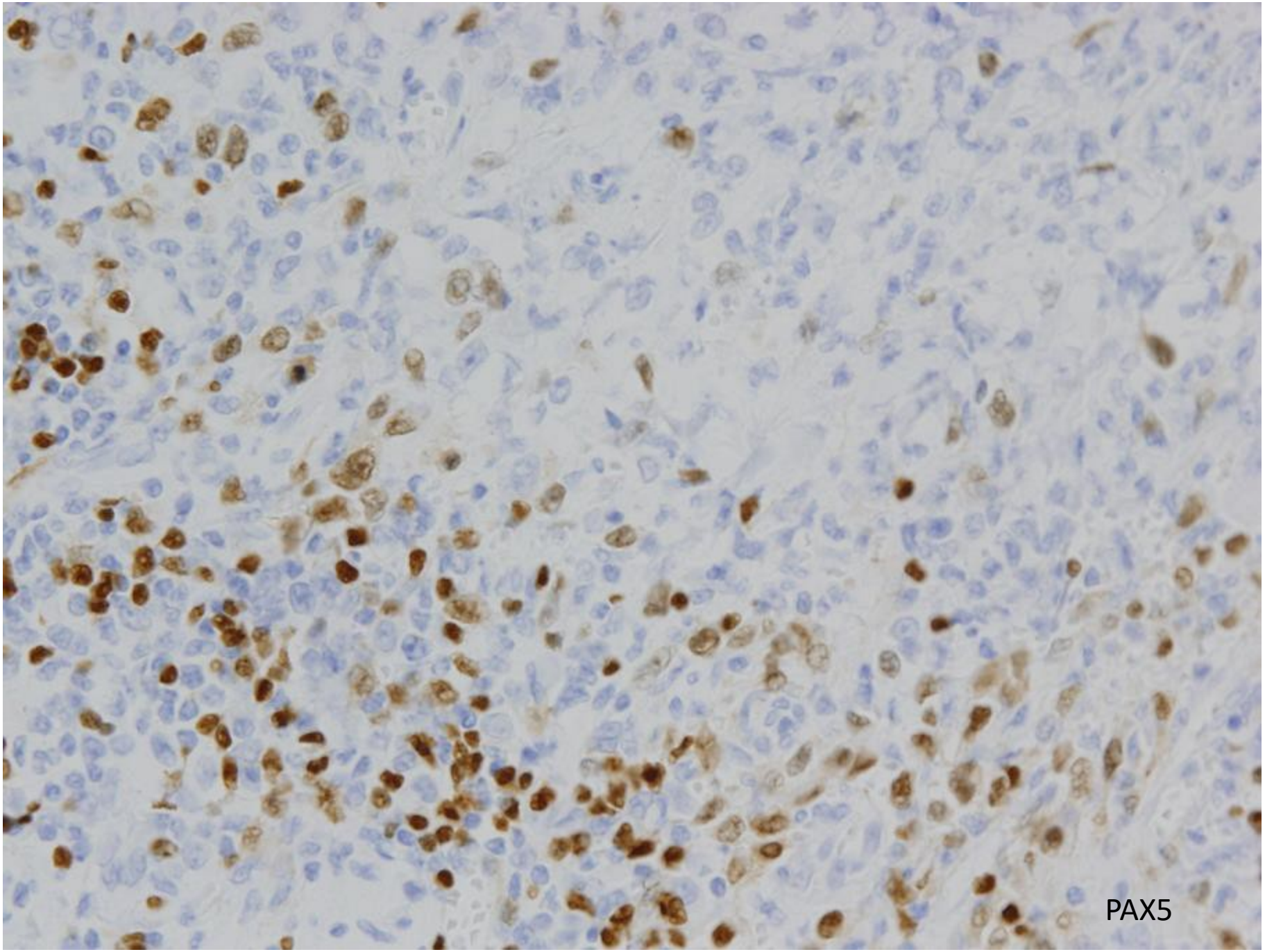
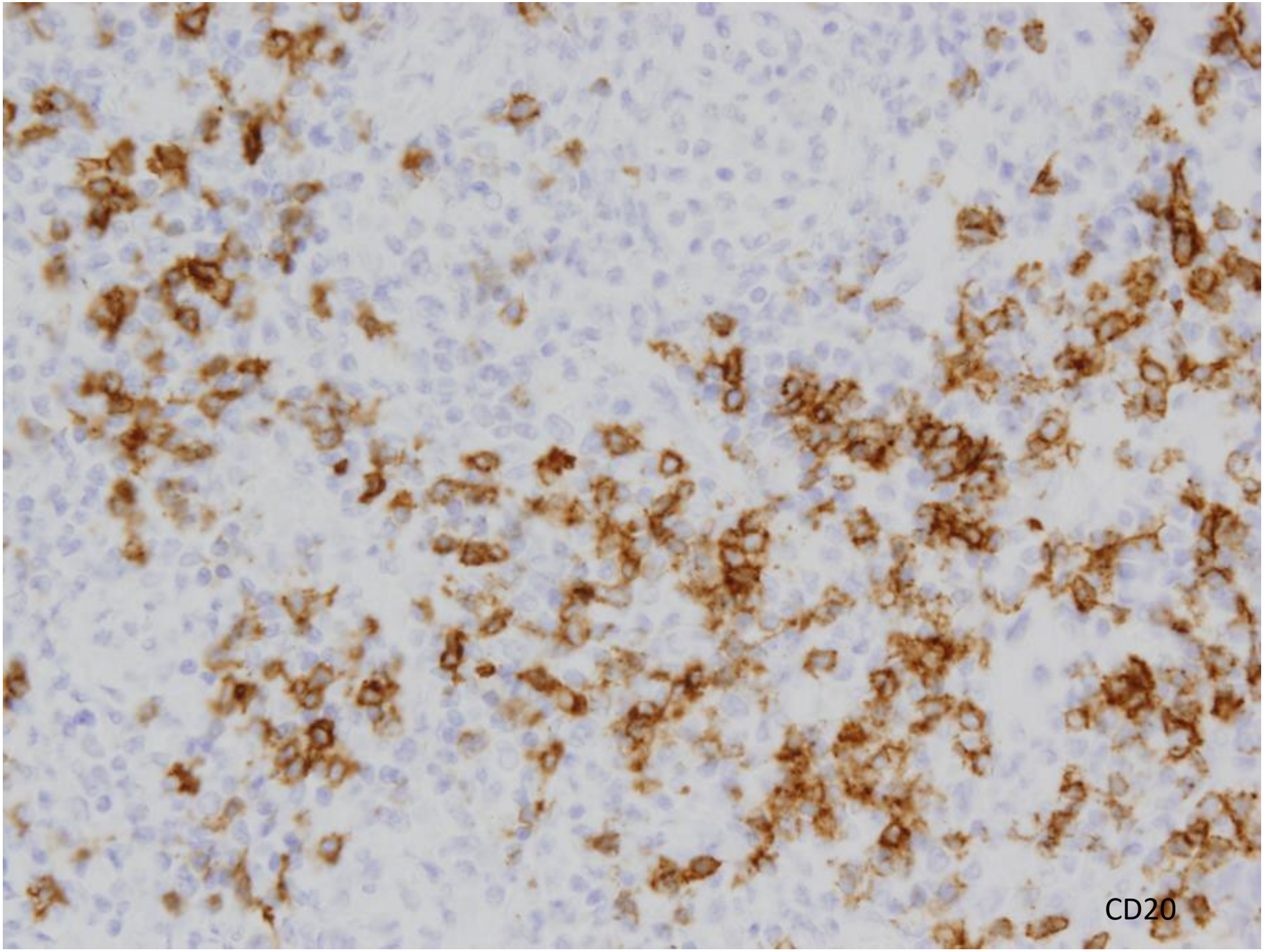

EBV-LMP


CD56


PAX5


CD20

Polymorphic PTLD

- Polymorphic (P) PTLD are composed of a heterogeneous population of immunoblasts, plasma cells and small and intermediate-sized lymphoid cells that efface the architecture of lymph nodes or form destructive extranodal masses and do not fulfill the criteria for any of the recognized types of lymphoma described in immunocompetent hosts.

- Difficulties in the recognition of:

  Forid IM PTLD with marked architectural distortion

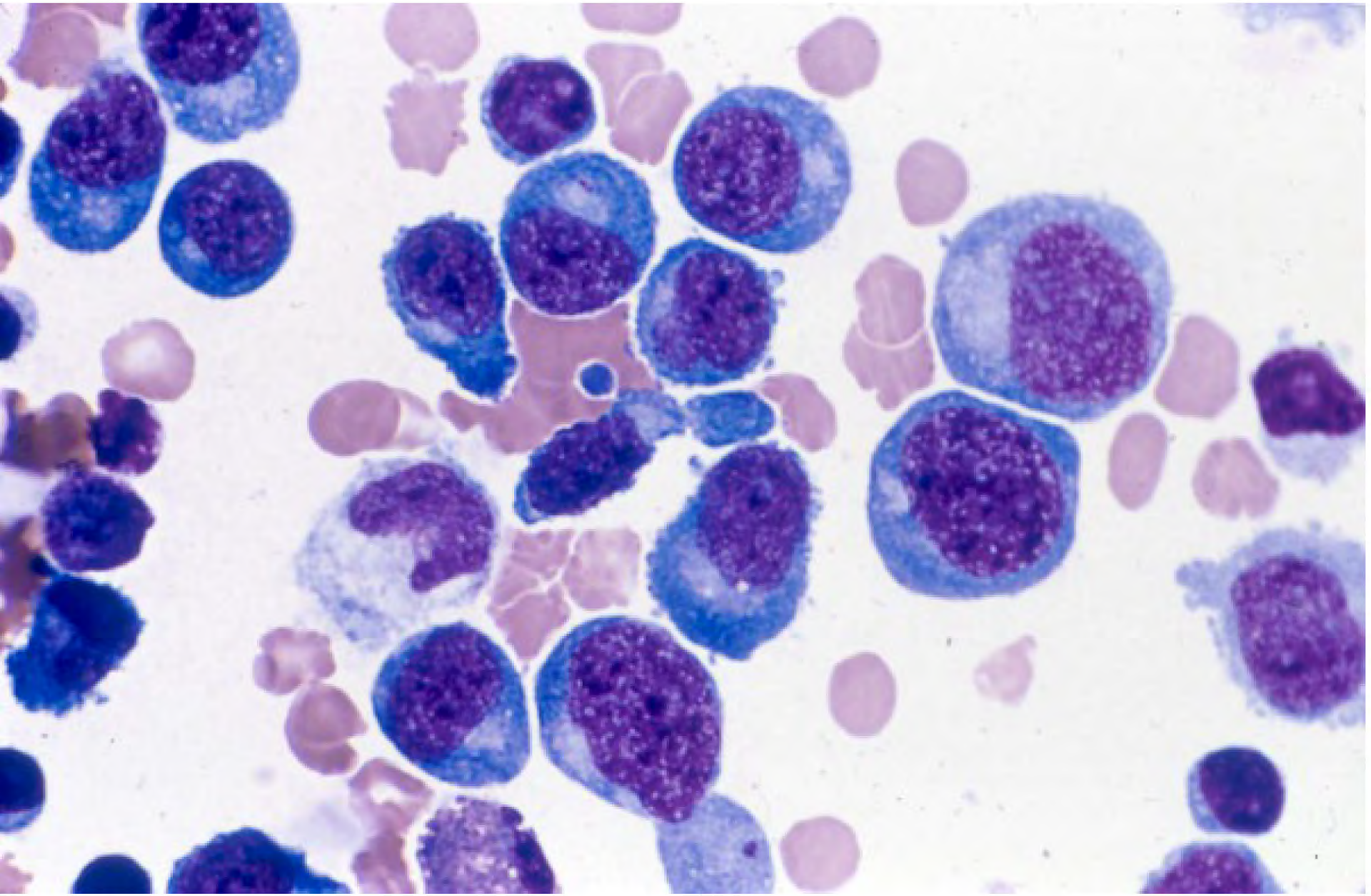
  Monomorphous PTLD with plasmacytic differentiation

- PTLD that fulfill the criteria for a T-cell histiocyte rich large B-cell lymphoma or an EBV+ DLBCL, NOS, which may appear polymorphic, are best considered a form of M-PTLD since they would be diagnosed as lymphoma in a non-transplant patient.

- Cases of monomorphic T-cell PTLD, which can also appear very polymorphic, must not be confused with P-PTLD.

Case 9

45 yrs old male
Pulmonary transplant
Pericardial and pleural effusion

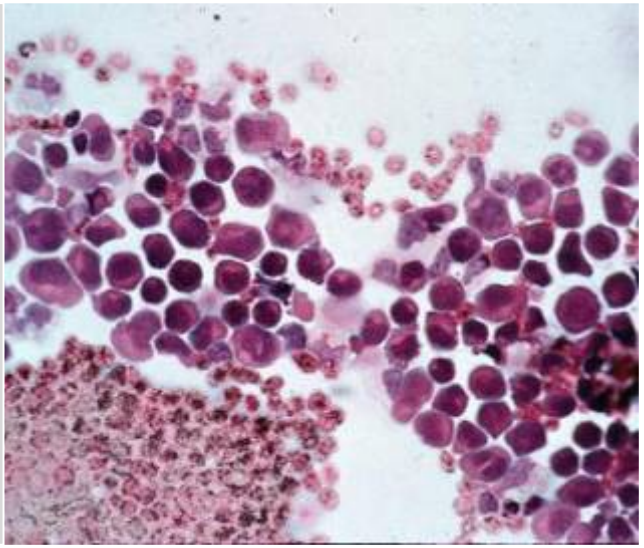


PEL:
Primary effusion lymphoma

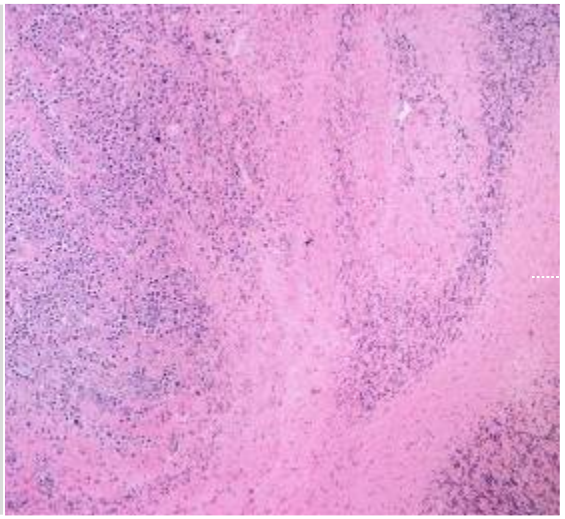
Primary Effusion Lymphoma

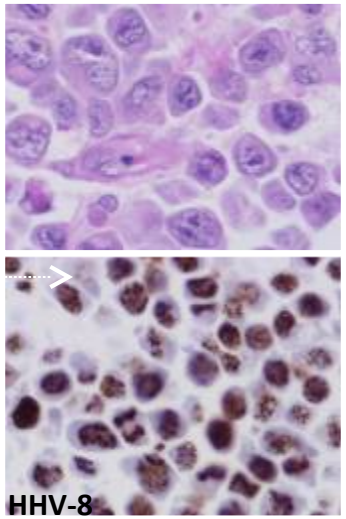
Clinical presentation

- HIV+ patients, Occasional HIV -
- Cavity Effusion
- Solid tumors: Gastrointestinal
- Rapid clinical course, median survival 5 months



- CD30, CD38, CD138, EMA +
- Mature B-cell markers -, Ig -/+,
- HHV-8 +, EBV +/-
- Occasional biphenotypic and bigenotypic (B & T)





Primary Effusion Lymphoma

- Most cases are associated with immunodeficiency, usually in patients infected with the human immunodeficiency virus HIV.

- In AIDS patients there is co-infection with the Epstein-Barr virus (EBV), although EBV is not required for the pathogenesis.

- PEL have been reported in other immunodeficiency states including post transplantation, and in patients with chronic viral hepatitis.

- PEL also occurs in elderly patients mostly from regions with a high prevalence of HHV8 such as the Mediterranean.

- Most patients present with malignant effusions involving a single body cavity, most often malignant pleural effusion or ascites.

- There is usually no lymphadenopathy or hepatosplenomegaly. Less commonly more than one cavity may be affected at presentation, and some patients may have a mass lesion associated with the effusion.

- A subset of patients have other manifestations of KSHV infection including Kaposi's sarcoma or multicentric Caslteman's disease