NON-CUTANEOUS EXTRA-NODAL MARGINAL ZONE LYMPHOMAS AND ITS DIFFERENTIALS

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MARGINAL ZONE LYMPHOMAS

- Extranodal Marginal Zone Lymphoma of Mucosa Associated Lymphoid tissue (MALT lymphoma)
- Nodal Marginal Zone Lymphoma
- Splenic Marginal Zone Lymphoma

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  - Immunoproliferative Small Intestinal Disease (IPSID)
  - Primary Cutaneous Marginal Zone Lymphoma (WHO HAEM5)/Lymphoprolfierative Disorder (ICC)
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  - Immunoproliferative Small Intestinal Disease (IPSID)
  - Primary Cutaneous Marginal Zone Lymphoma (WHO HAEM5)/Lymphoprolfierative Disorder (ICC)
    - Class-Swiched (76-86%)
      - Most IgG (IgG4 in 40%)
    - Non-Class-Switched
      - More associated with extra-cutaneous spread
- Nodal Marginal Zone Lymphoma
- Splenic Marginal Zone Lymphoma

Mucosa Associated Lymphoid Tissue (MALT)

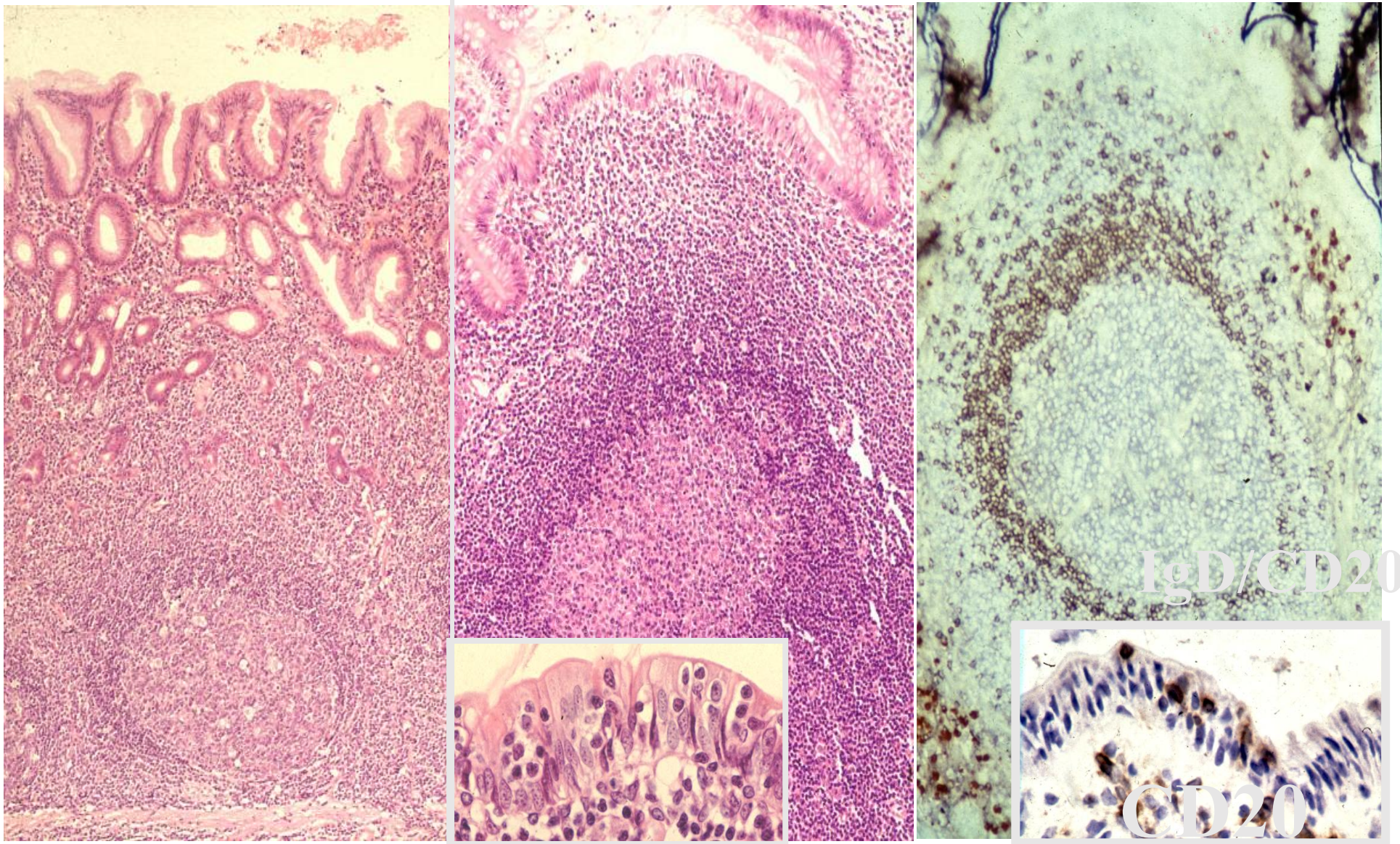
- Mucosae united by common immune system
- Mucosae may share common pool of lymphocytes that may circulate between sites
- Best exemplified by GALT (Peyer’s patch)

Mucosa Associated Lymphoid Tissue (MALT)

Best exemplified by GALT

Comprises

- Organised lymphoid tissue (Peyer's patch)
- Lamina propria (plasma cells, histiocytes)
- Intra-epithelial lymphocytes (CD4-/CD8+ T cells and B cells in the dome epithelium)
- Mesenteric lymph nodes



The human gut contains a novel population of B-lymphocytes which resemble marginal zone cells. Spencer J et al. Clin Exp Immunol 1985

Human Peyer's patches: an immunohistochemical study. Spencer J et al. Gut 1986

Malignant Lymphoma of Mucosa-Associated Lymphoid Tissue

A Distinctive Type of B-Cell Lymphoma

PETER ISAACSON, DM, MRC PATH, AND DENNIS H. WRIGHT, MD, FRC PATH

As illustrated in the two cases described in this paper close morphologic and immunohistochemical similarities exist between Mediterranean lymphoma (MTL) and primary gastrointestinal lymphoma of follicle center cell (FCC) origin as it occurs in Western countries. Similarities between the two conditions include a dense noninvasive monotypic lamina propria plasma cell infiltrate, present in all cases of MTL and in some cases of Western gastrointestinal FCC lymphoma, and an invasive infiltrate of FCCs morphologically distinct from the plasma cells. A distinctive lesion produced by individual gland invasion characterizes both types of lymphoma. A clonal relationship between the lamina propria plasma cells and the invasive FCCs, long suspected but never proved in MTL, can be demonstrated in Western cases. Many of the histologic and clinical features common to these lymphomas can be explained in the context of the normal maturation sequences of gut associated lymphoid tissue. It is suggested that MTL and Western cases of primary FCC gastrointestinal lymphoma share a common histogenesis from mucosa associated lymphoid tissue.

***Cancer* 52:1410–1416, 1983.**

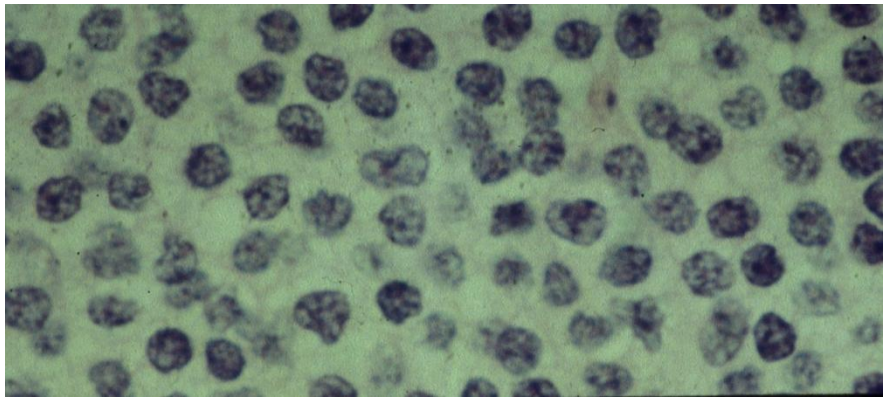
MALT Lymphoma

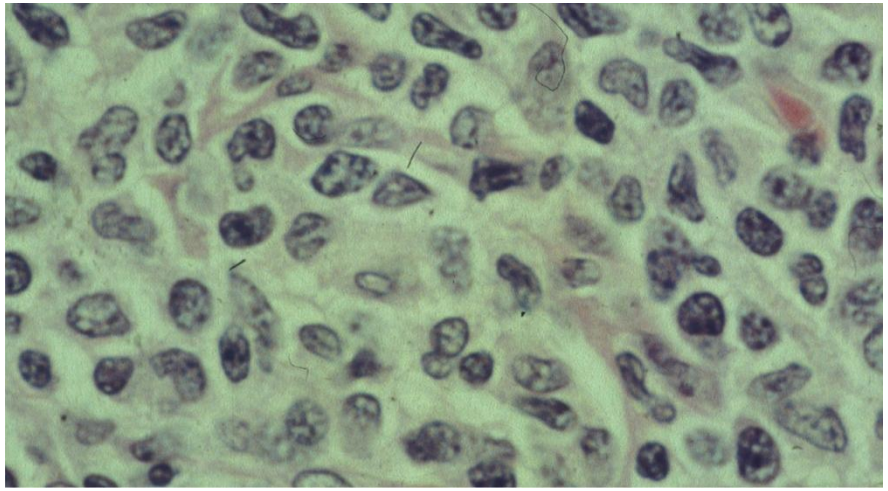
- Gastrointestinal tract
  - stomach
  - intestine (inc IPSID)
- Salivary gland
- Respiratory tract
  - lung
  - pharynx, larynx, trachea
- Thyroid
- Ocular adnexa
  - conjunctiva
  - lacrimal gland
  - orbit*
- Thymus
- Liver
- Genitourinary tract
  - bladder
  - prostate
  - kidney
- Breast
- Skin*
- Dura*
- Rare sites

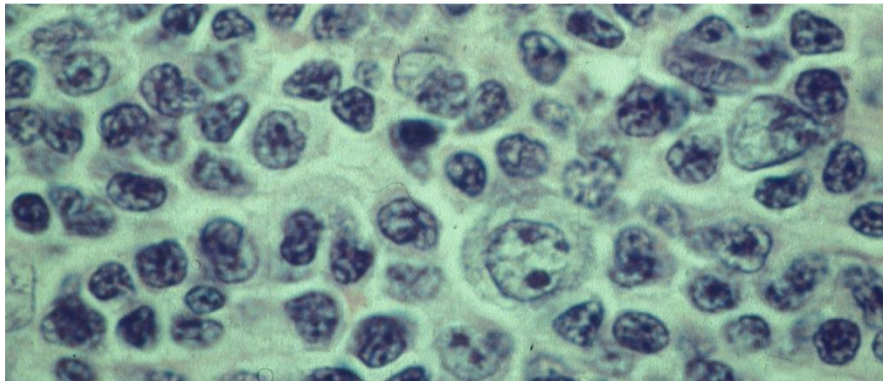
*not mucosal

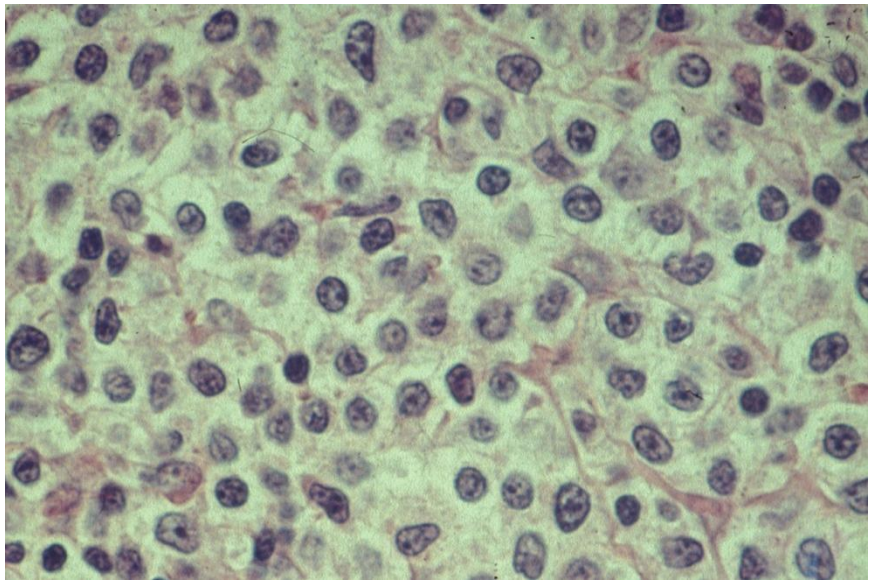
Site of disease	Proportion of cases[a]
Gastrointestinal tract	
Stomach	30%
Colon/rectum	5%
Small intestine	3%
Ocular adnexa/orbit	12%
Skin	10%
Lung	9%
Salivary glands	7%
Breast	3%
Thyroid gland	2%
Oral cavity/oropharynx	2%
Soft tissue	2%
Genitourinary tract (kidney, bladder, prostate gland)	1%
Nasopharynx	1%
Other sites	13%

From: The international Consensus Classification of Myeloid and Lymphoid Neoplasms
Arber DA et al

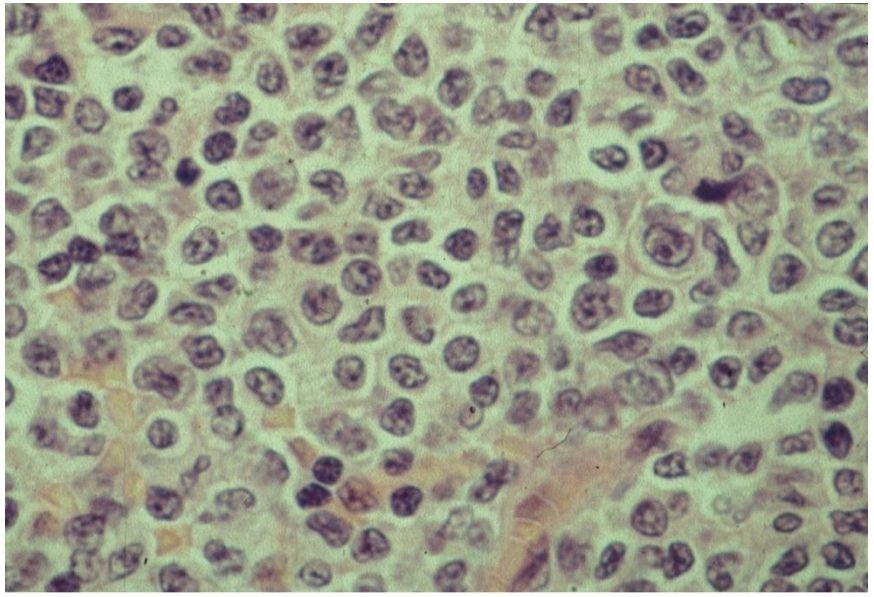


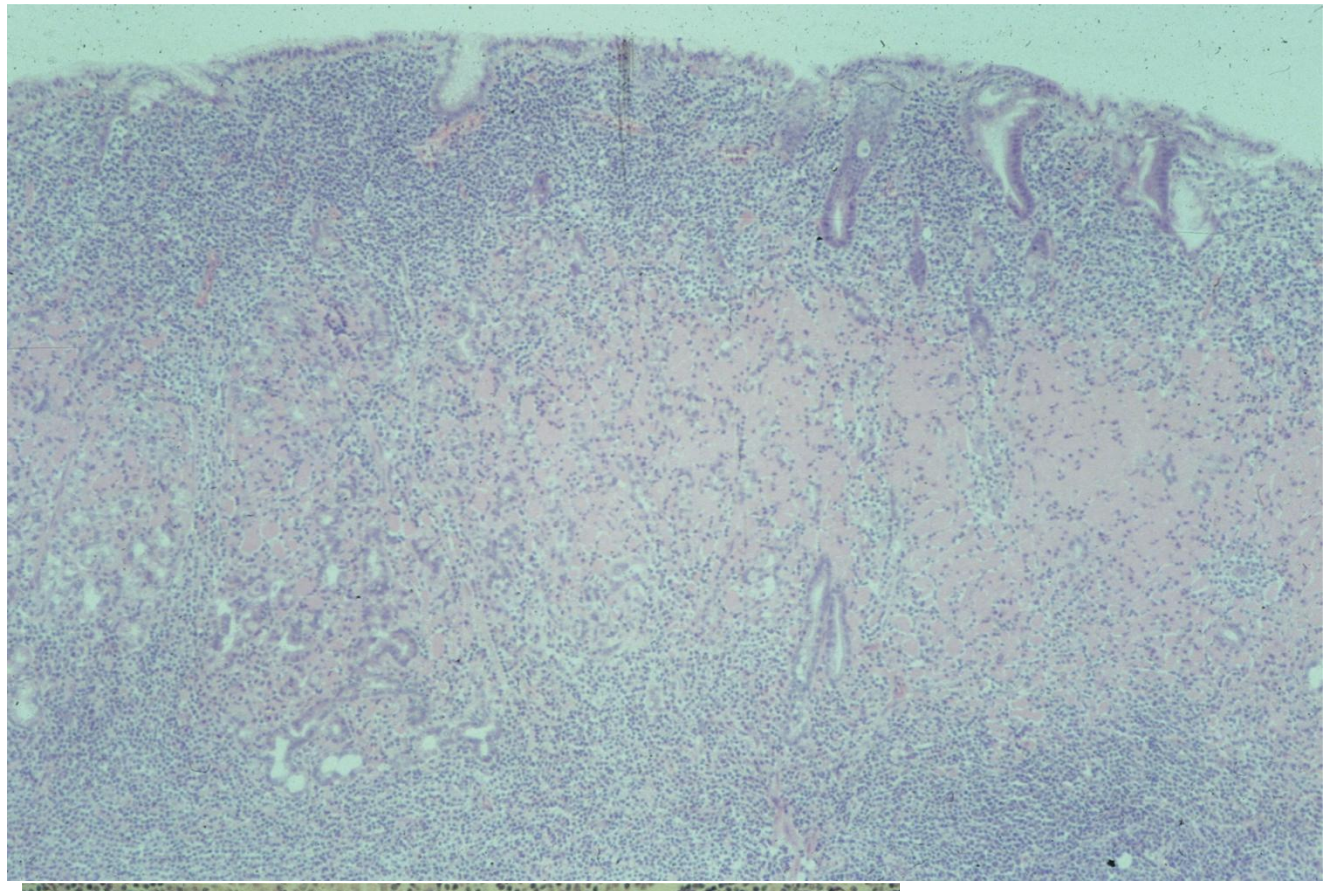


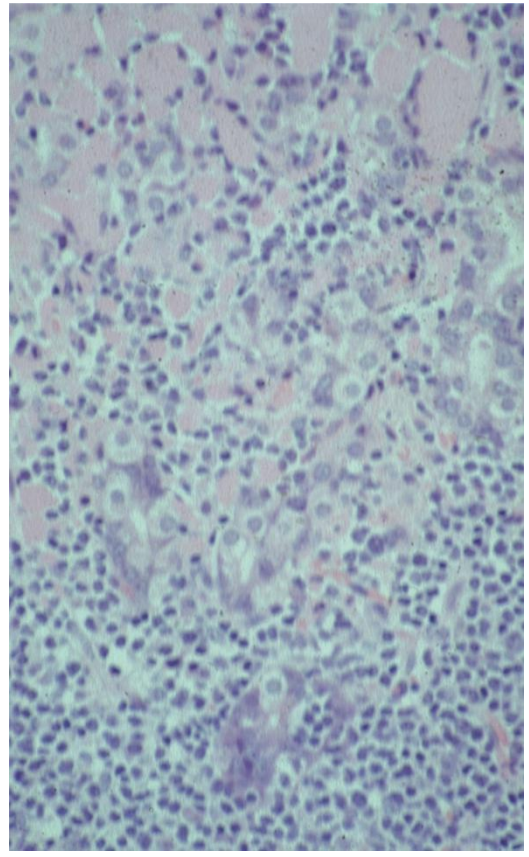


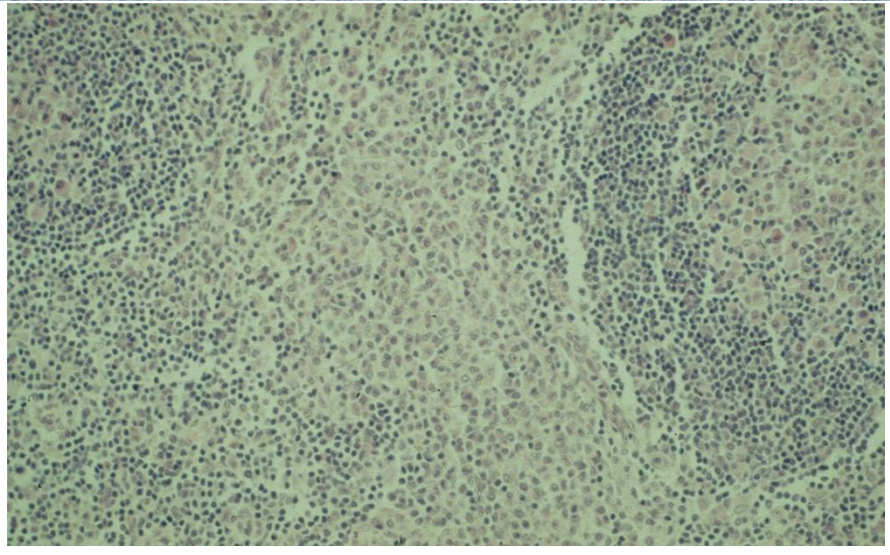


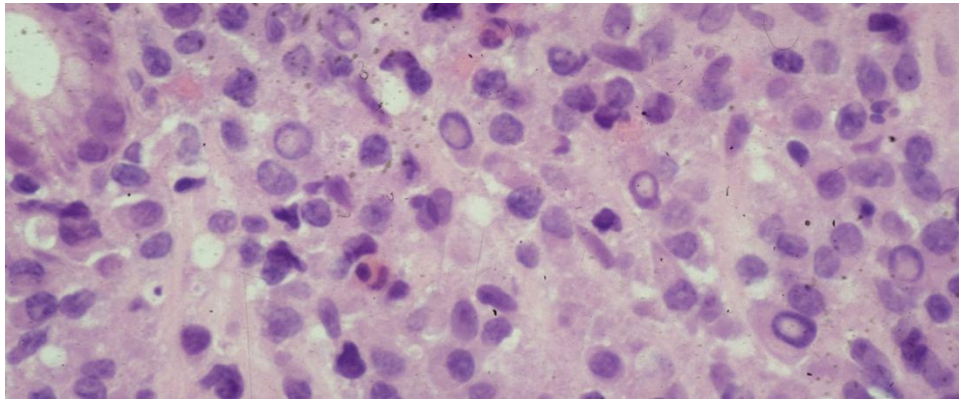
Centrocyte like cell morphology

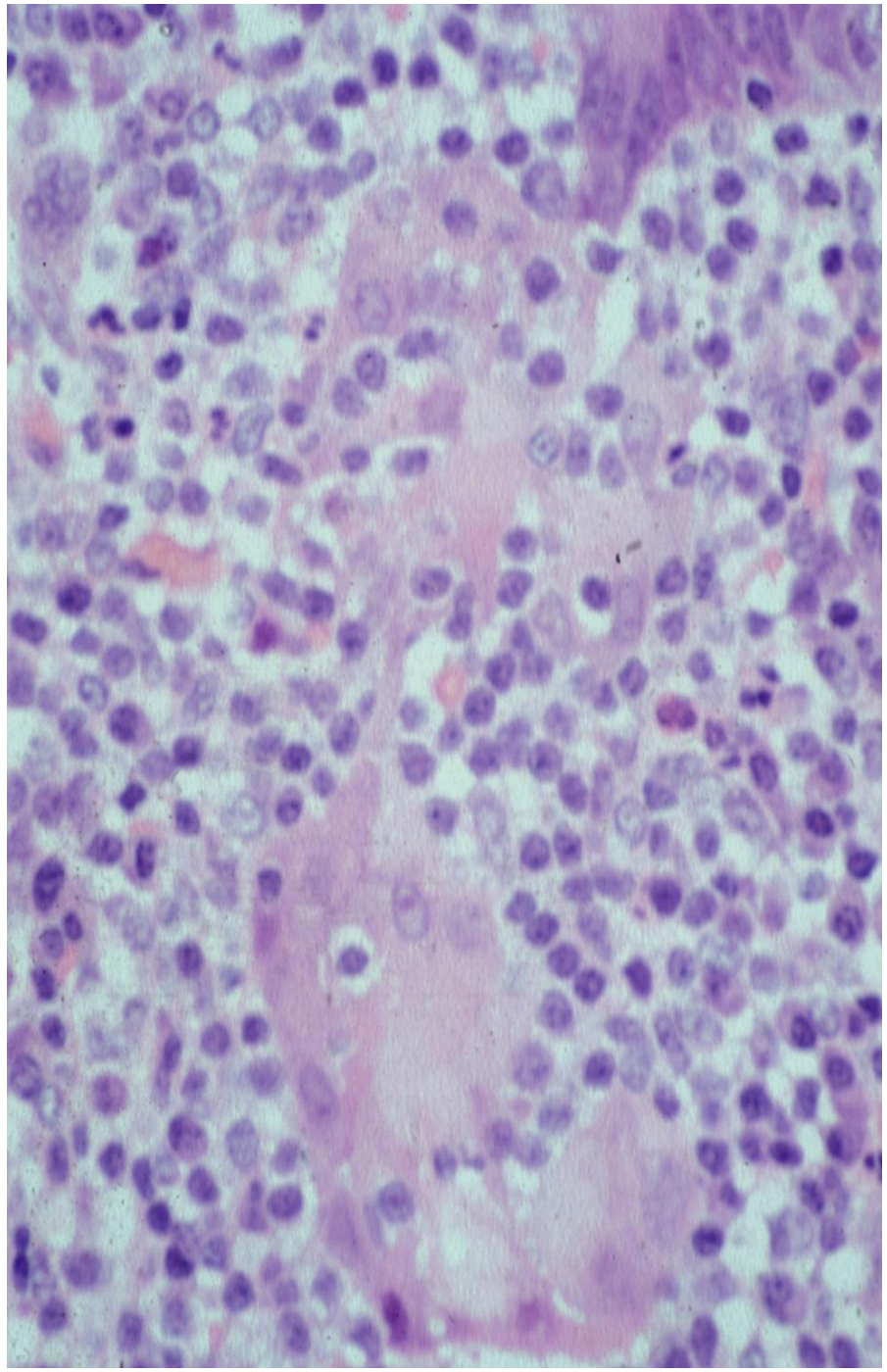


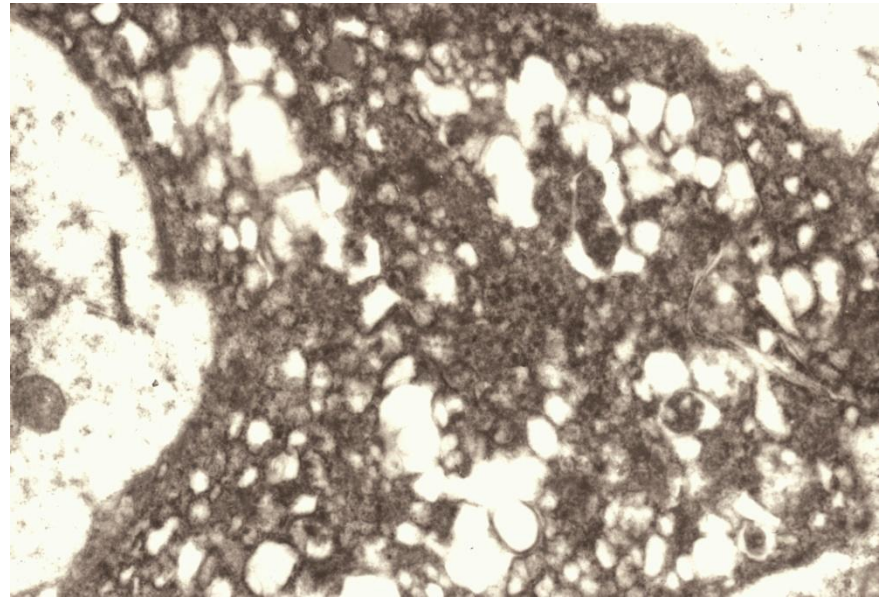


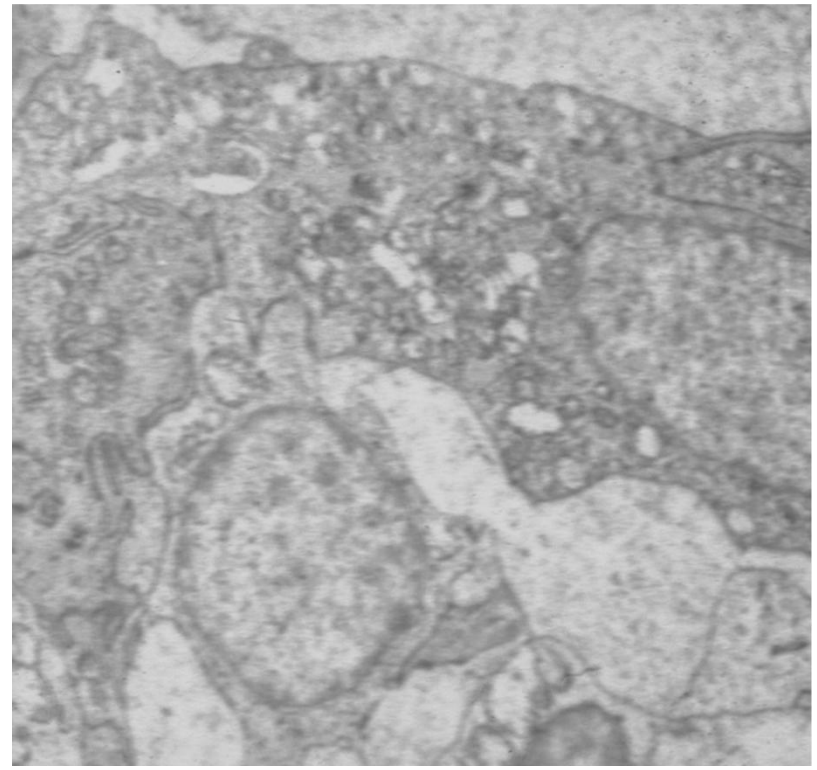


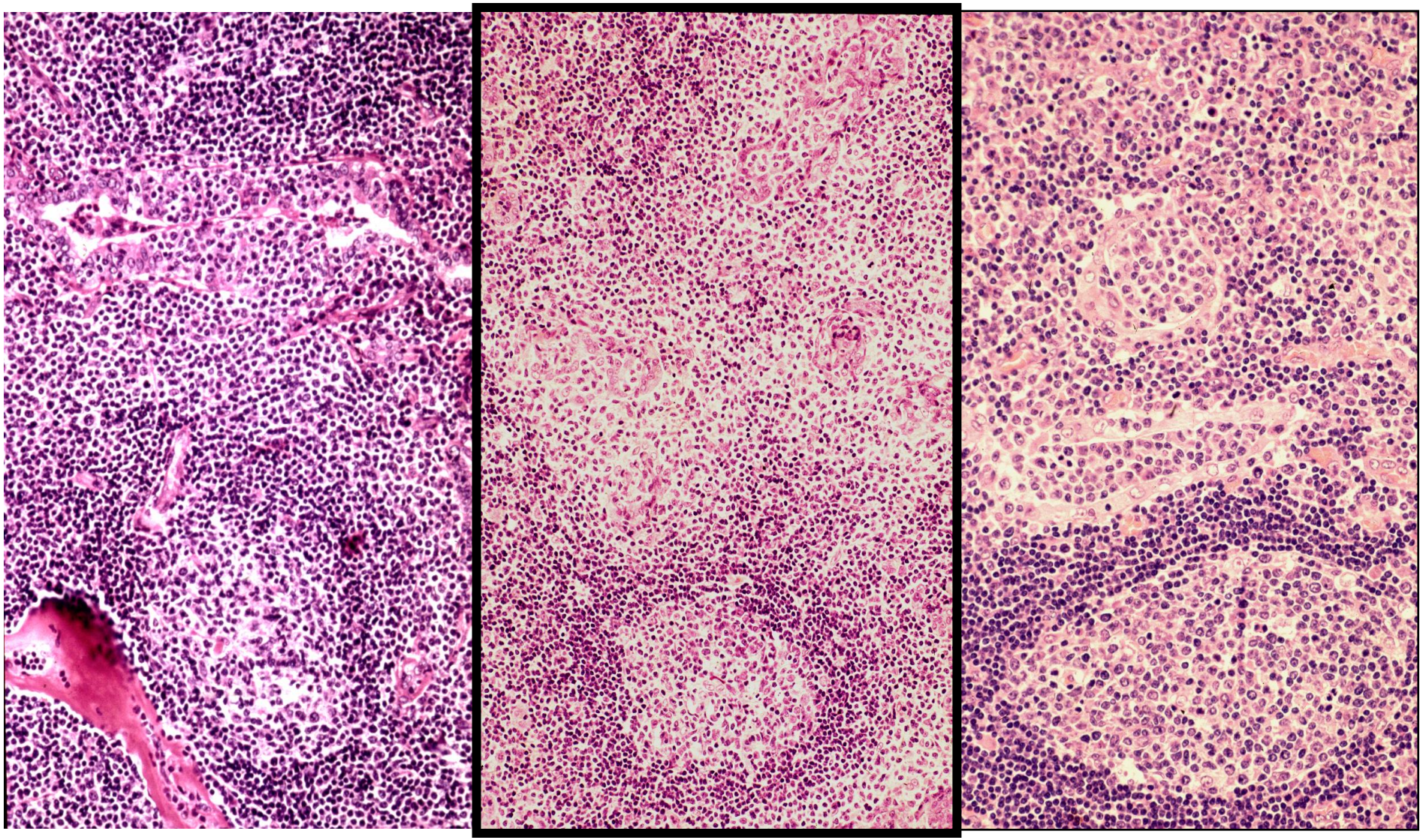






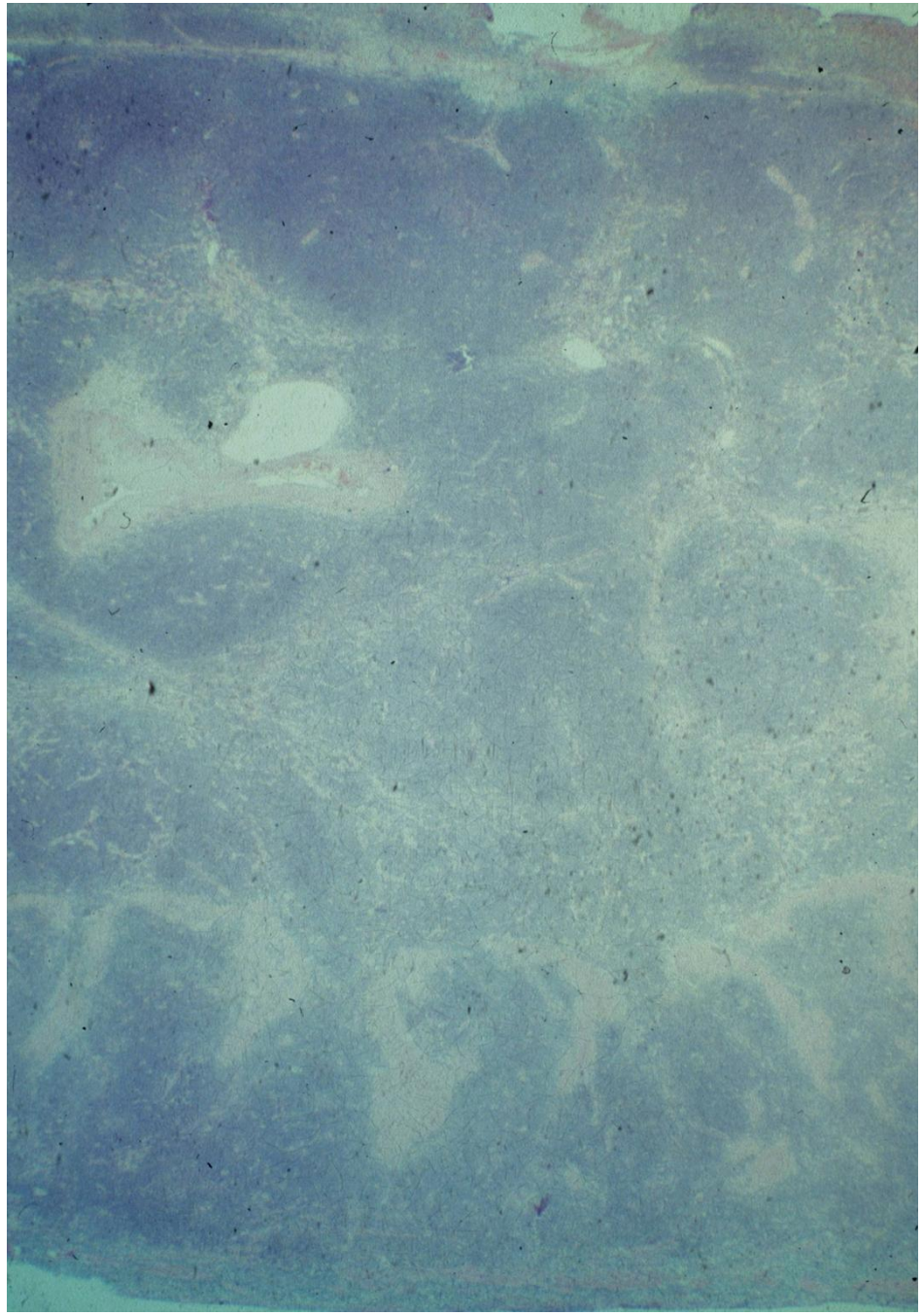


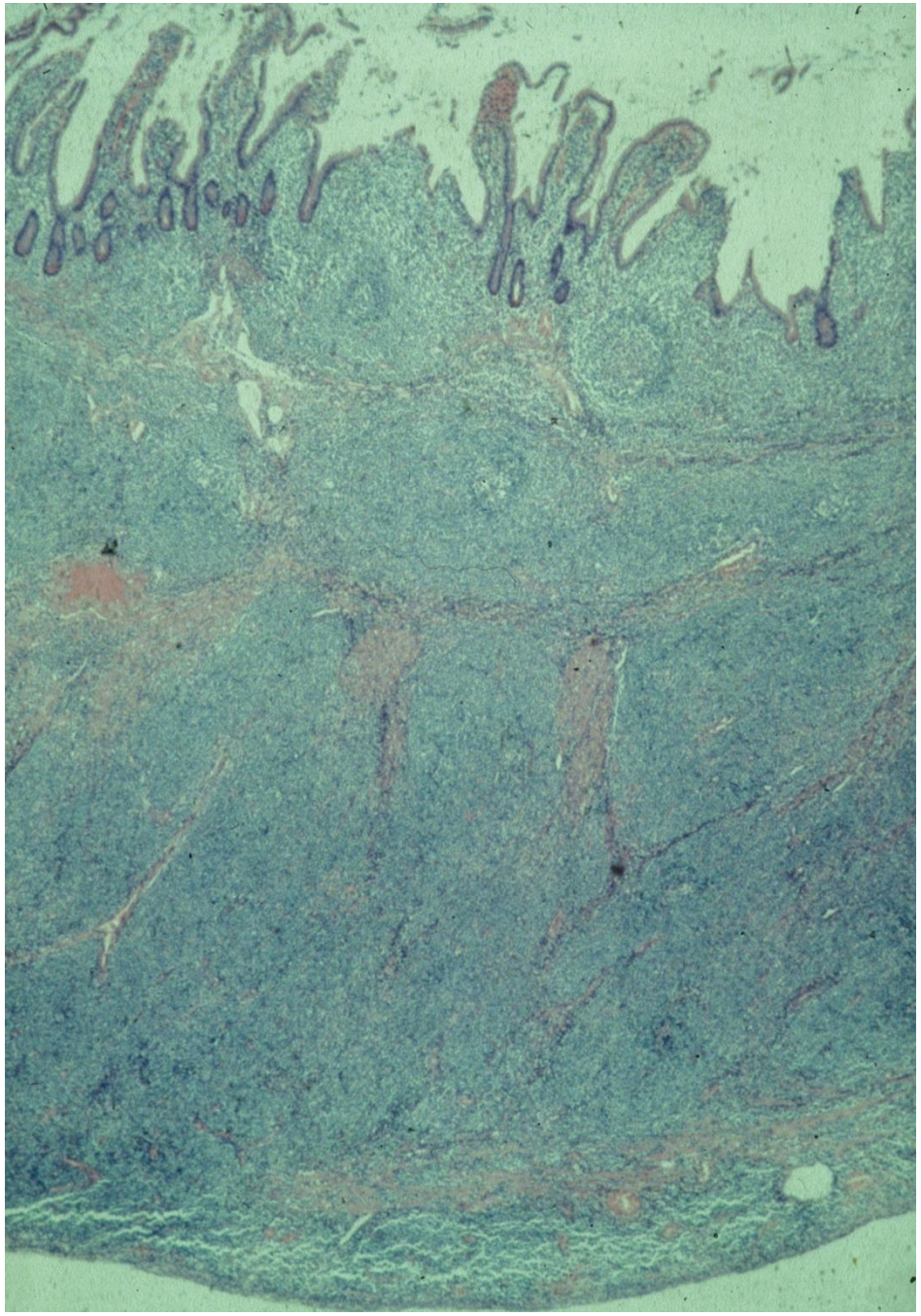


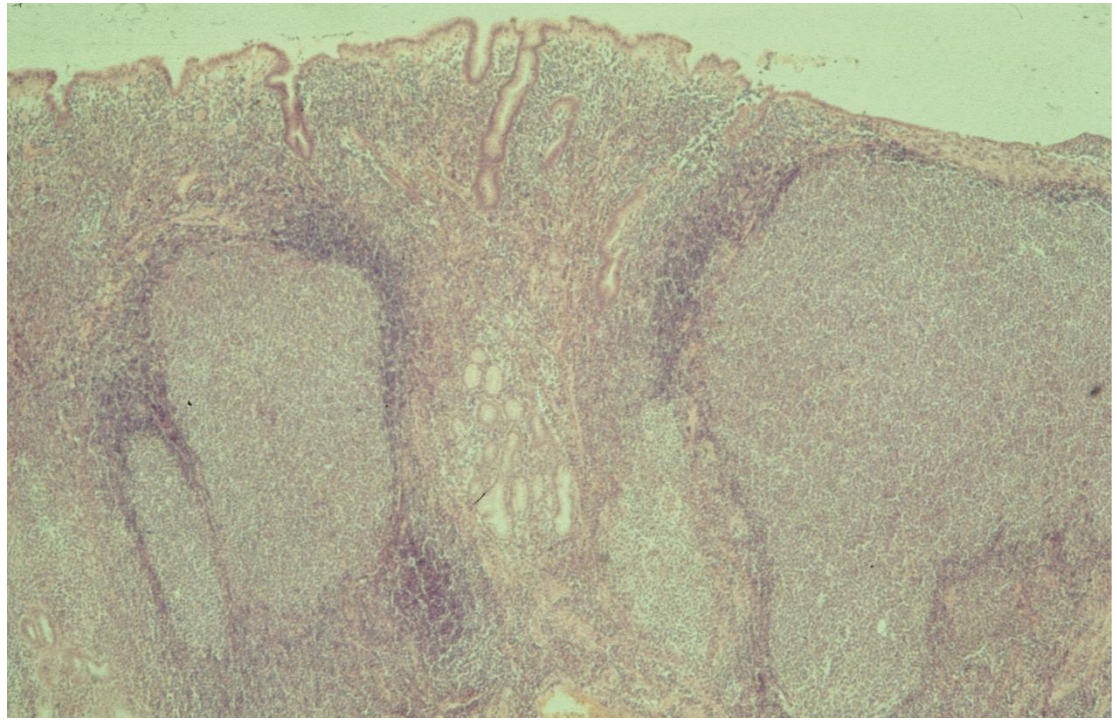


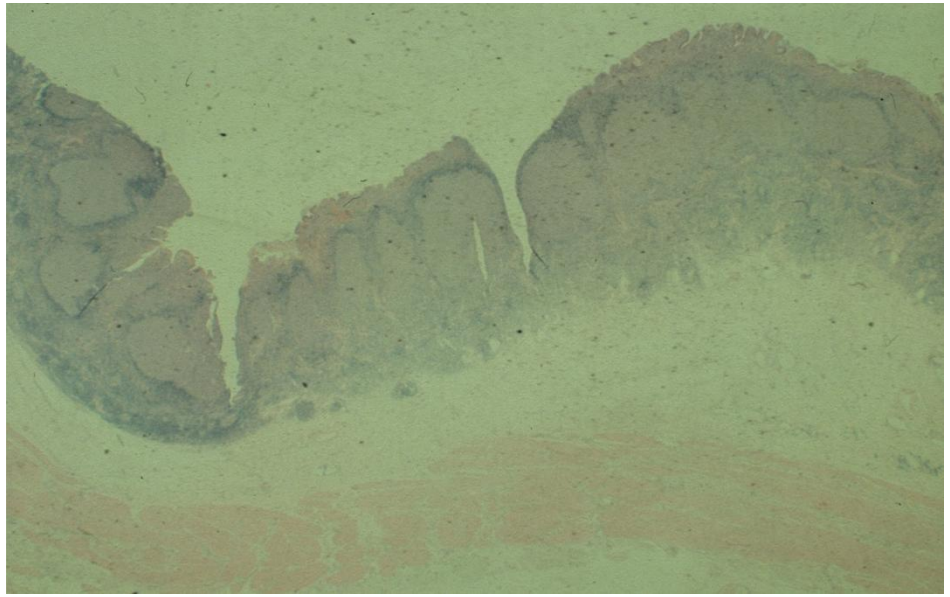
Lung **Salivary Gland** **Thyroid**

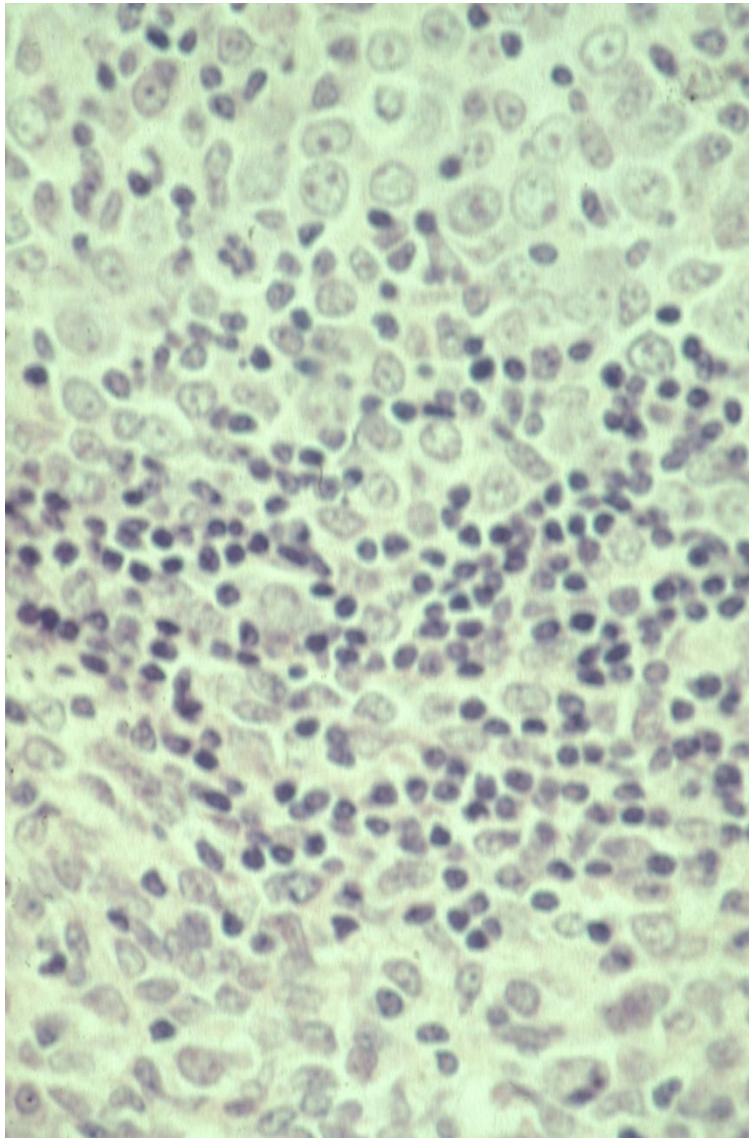
Isaacson P and Wright DH. Cancer 1984











MALT Lymphoma

Immunophenotype

- Positive for B cell markers CD20 and CD79a
- Negative for CD10 and bcl-6
- Usually CD5 negative
- Negative for CD23 and cyclinD1
- Express bcl-2
- Underlying FDC meshwork

CD43 (MT1)

- T lineage-associated marker
- Negative in the majority of non-neoplastic B cells (except plasma cells and rare lymphoplasmacytoid cells)
- Present in some B cell lymphomas (particularly histologically low grade B cell lymphomas)
  - Mantle cell lymphoma
  - Small lymphocytic lymphoma/chronic lymphocytic leukaemia
  - Follicular lymphoma (10%)

  - Burkitt lymphoma
  - Diffuse large B cell lymphoma (10-20%)

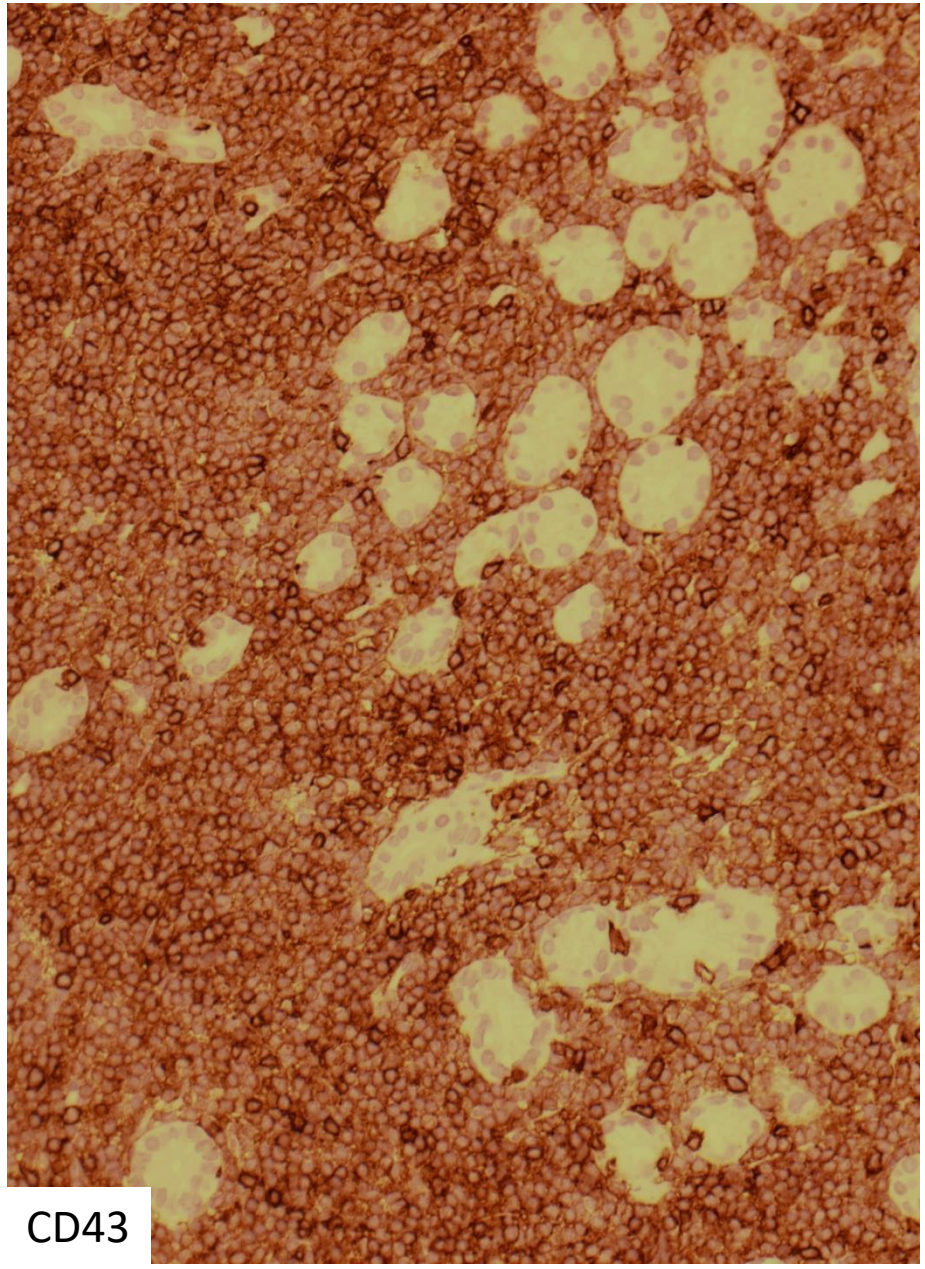
MALT LYMPHOMA

- Immunophenotype
  - CD43
    - Present in ± 50% MALT lymphoma
    - May be seen in LESA (MESA)

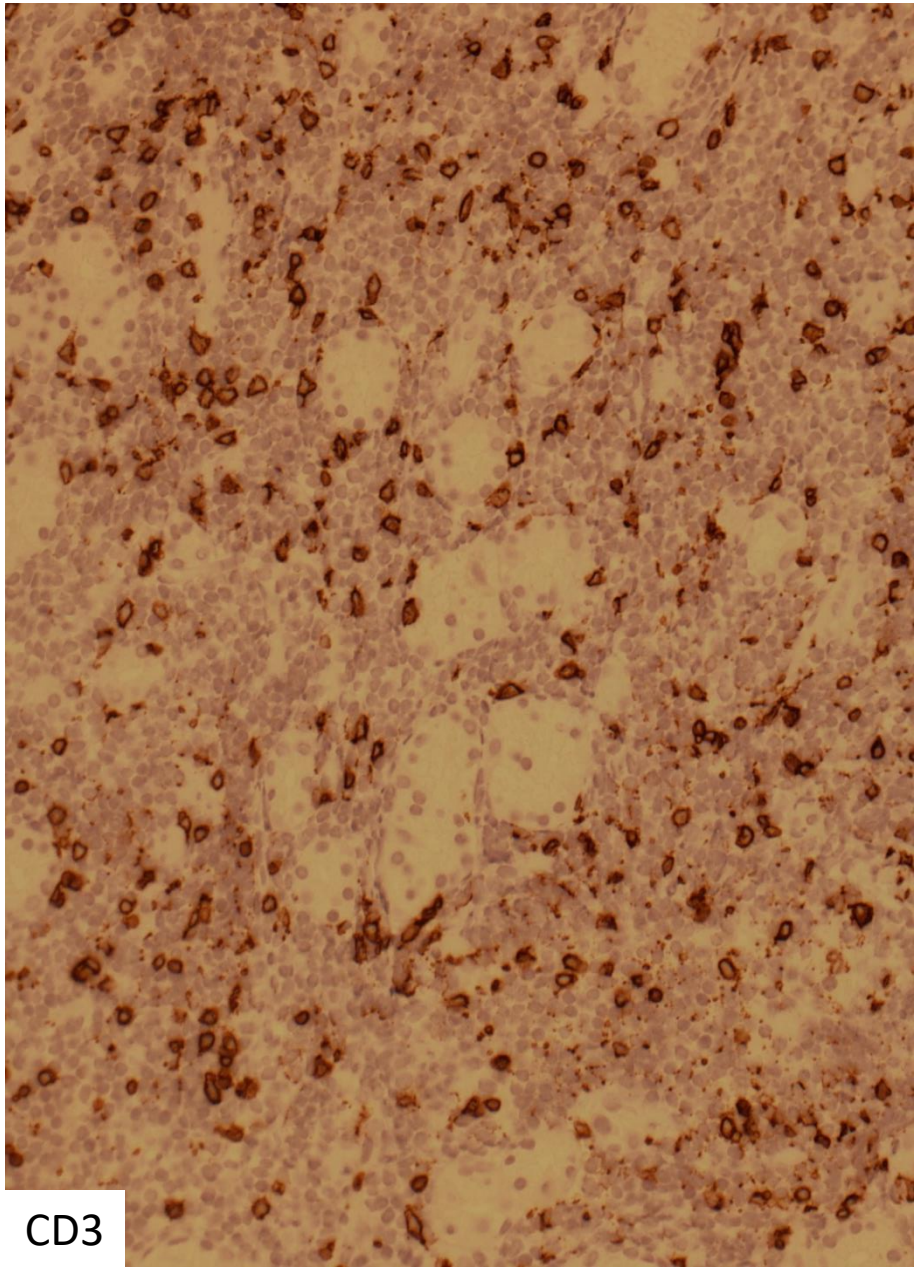
    Qintana PG et al Hum Pathol 1997; 28: 850-861

      - In up to 42% of bLEL
    - Atypical marginal zone hyperplasia

    Attygalle AD et al BLOOD 2004; 104: 3343-3348



CD43



CD3

CD5+ MALT lymphoma

- More frequent in head/neck and ocular regions – 10/13
- Frequent BM/PB involved – 5/13
- Early recurrence or dissemination – 4/13

Cook & Pugh Mod Pathol 1994 (abstract)
Ferry et al AJCP 1996
Ueda et al Virchows Arch 1996
Ballesteros et al AJSP 1998
Wenzel et al Leuk Lymphoma 2001
Heuring et al Br J Ophthalmol 2001
Tasaki et al Pathol Int 2007

Histological grading of gastric MALT lymphoma

106 patients

Group A	LG	No custers or groups of > 5 large cells
Group B	LG + HG	Intermingled cells <10%
Group C	HG + LG	Large clusters >20 large cells or >10% large cells with residual LG component
Group D	HG	Pure large cell population

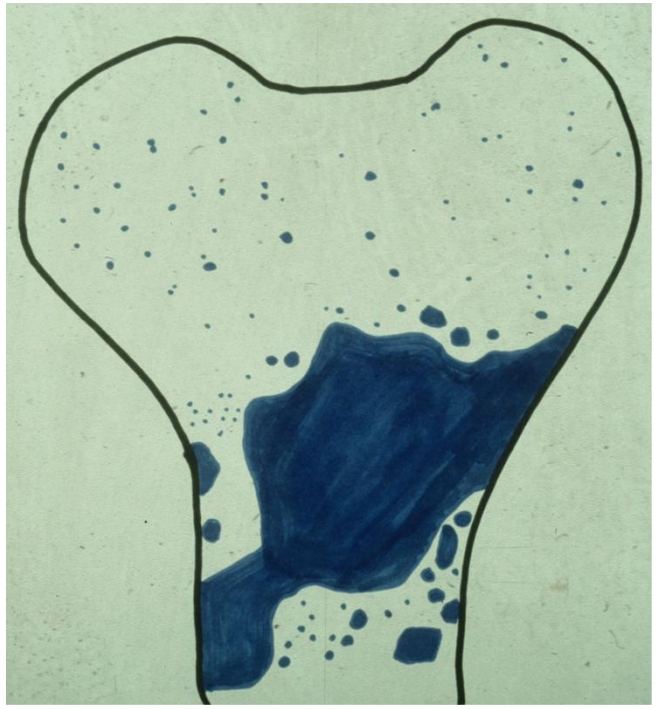
De Jong et al Gastroenterol 1997

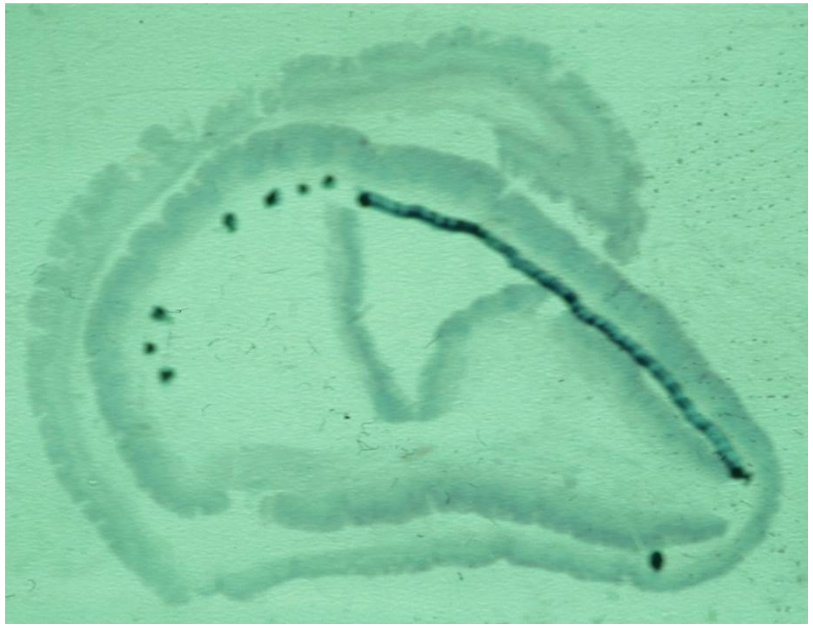
Histological grading of gastric MALT lymphoma

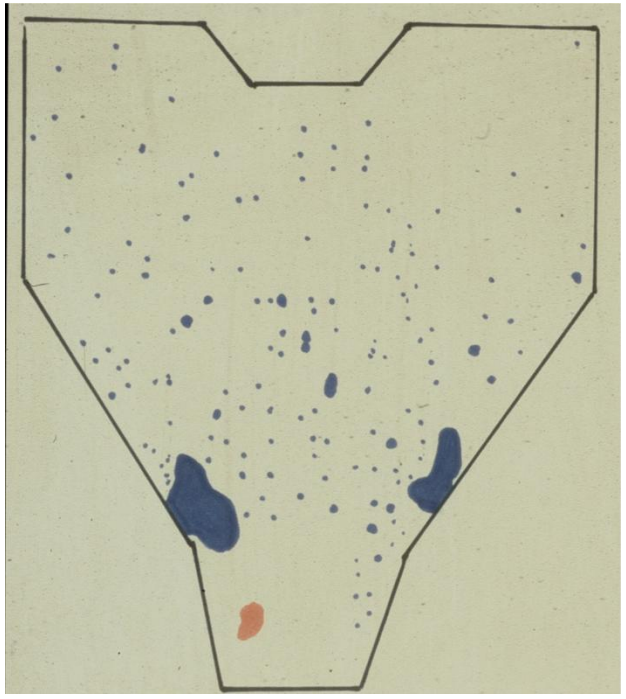
	overall survival	
	5yr	**10yr**
Group A	95%	95%
Group B	64%	53%
Group C	46%	46%
Group D	35%	29%

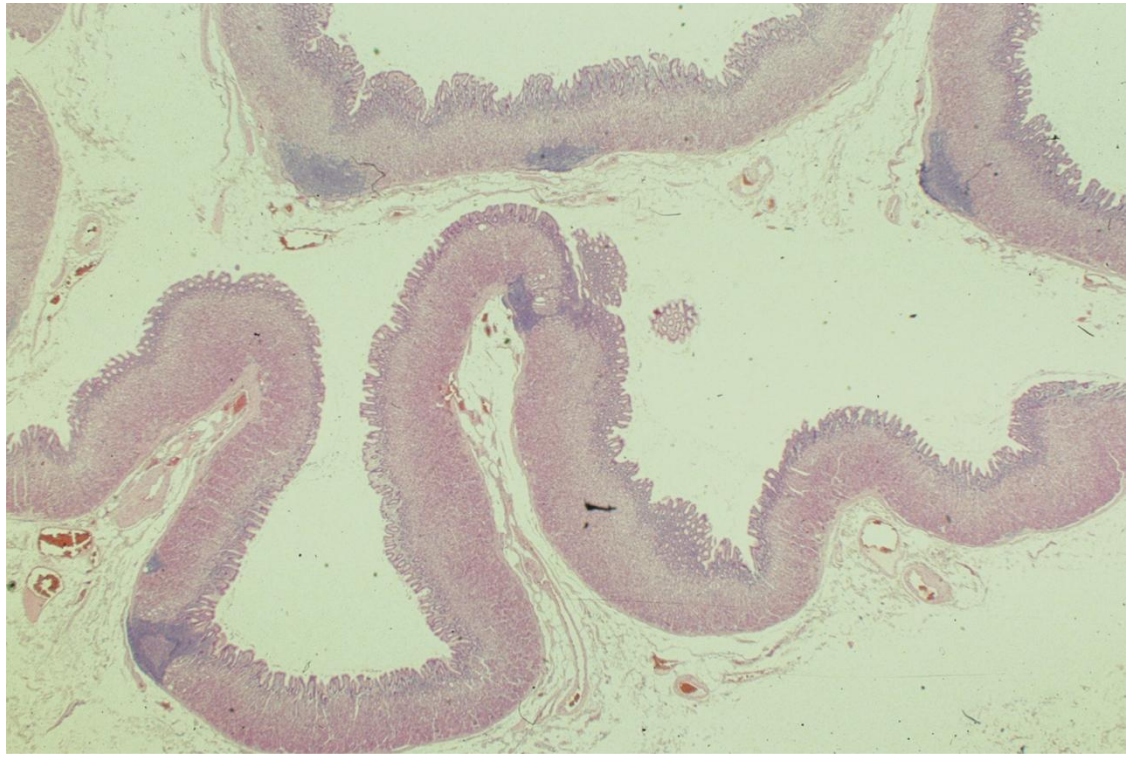
	Disease specific survival	
	5yr	**10yr**
Group A	95%	95%
Group B	90%	75%
Group C	46%	46%
Group D	44%	36%

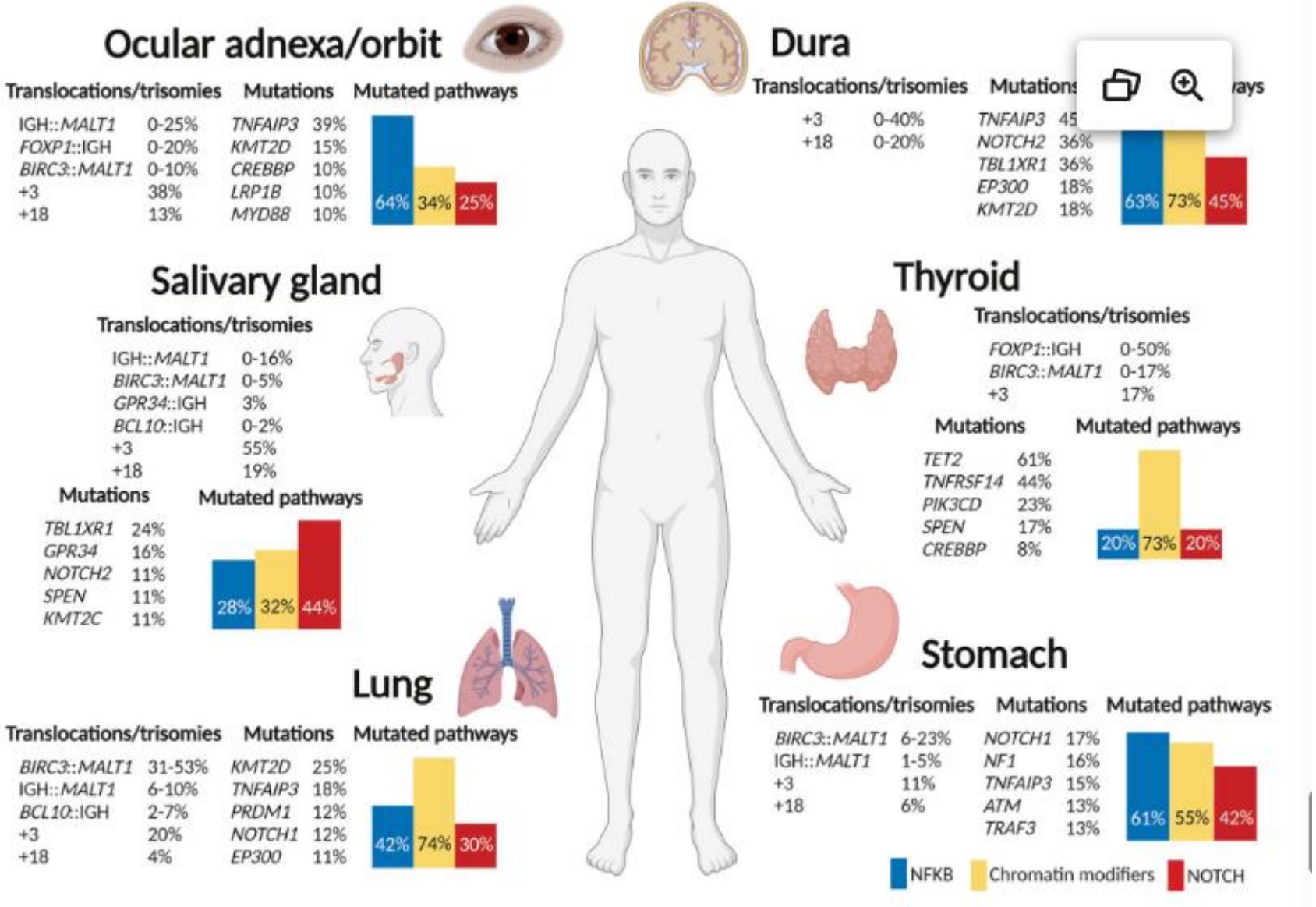
De Jong et al Gastroenterol 1997



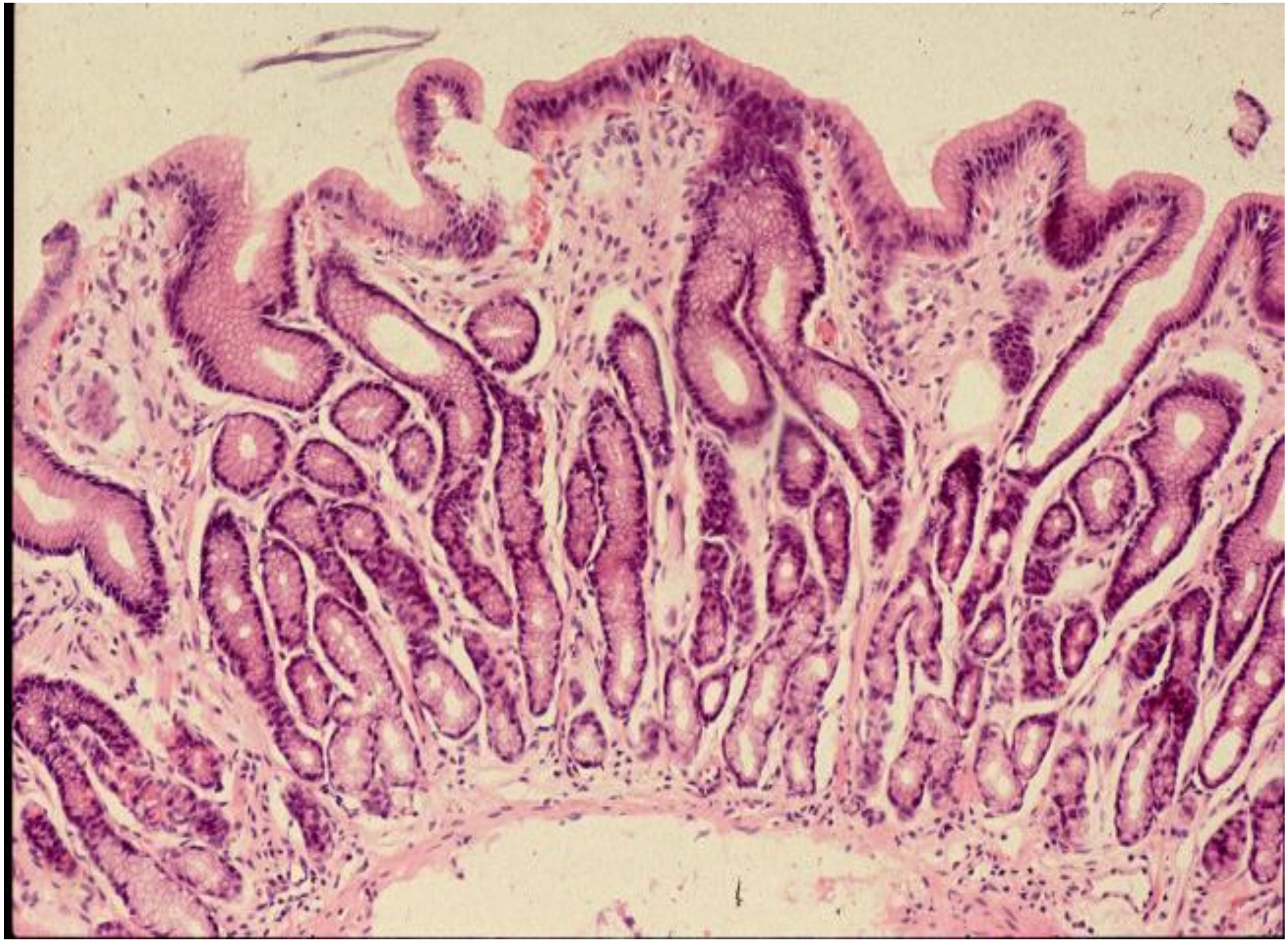






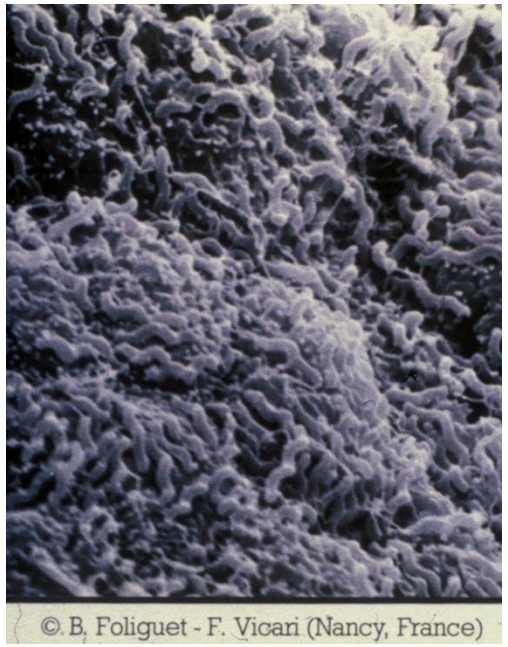


From: The international Consensus Classification of Myeloid and Lymphoid Neoplasms
Arber DA et al



ACQUISITION OF LYMPHOID FOLLICLES

- Helicobacter
  - Helicobacter pylori
  - Helicobacter Heilmannii
- Autoimmune disease
- Others
  - Coeliac disease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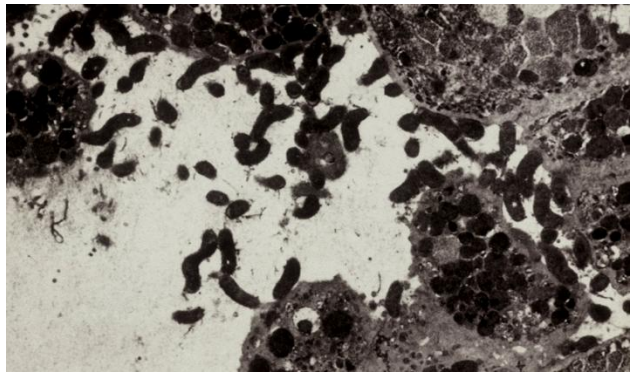
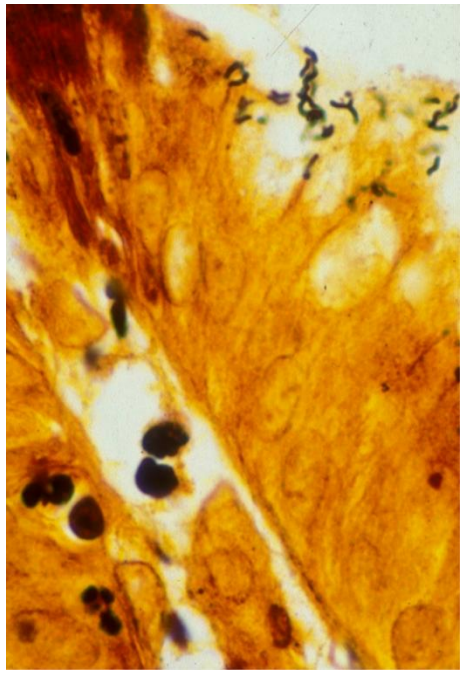
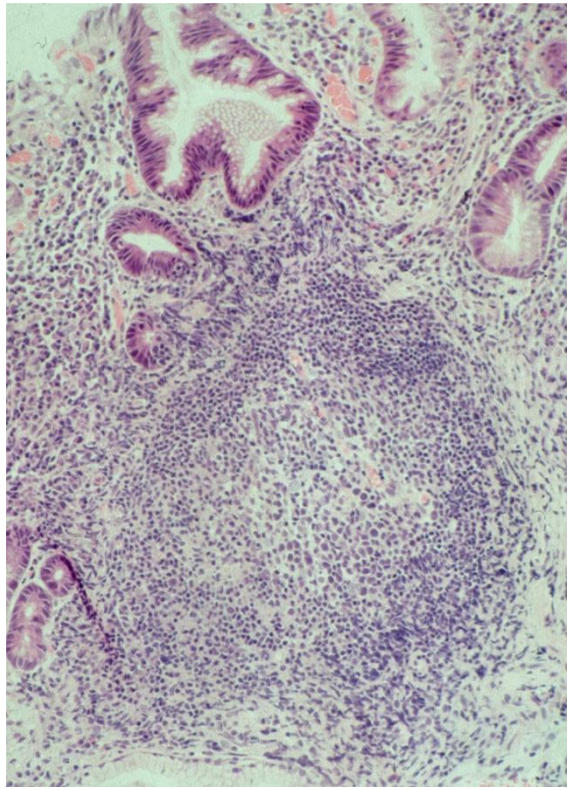
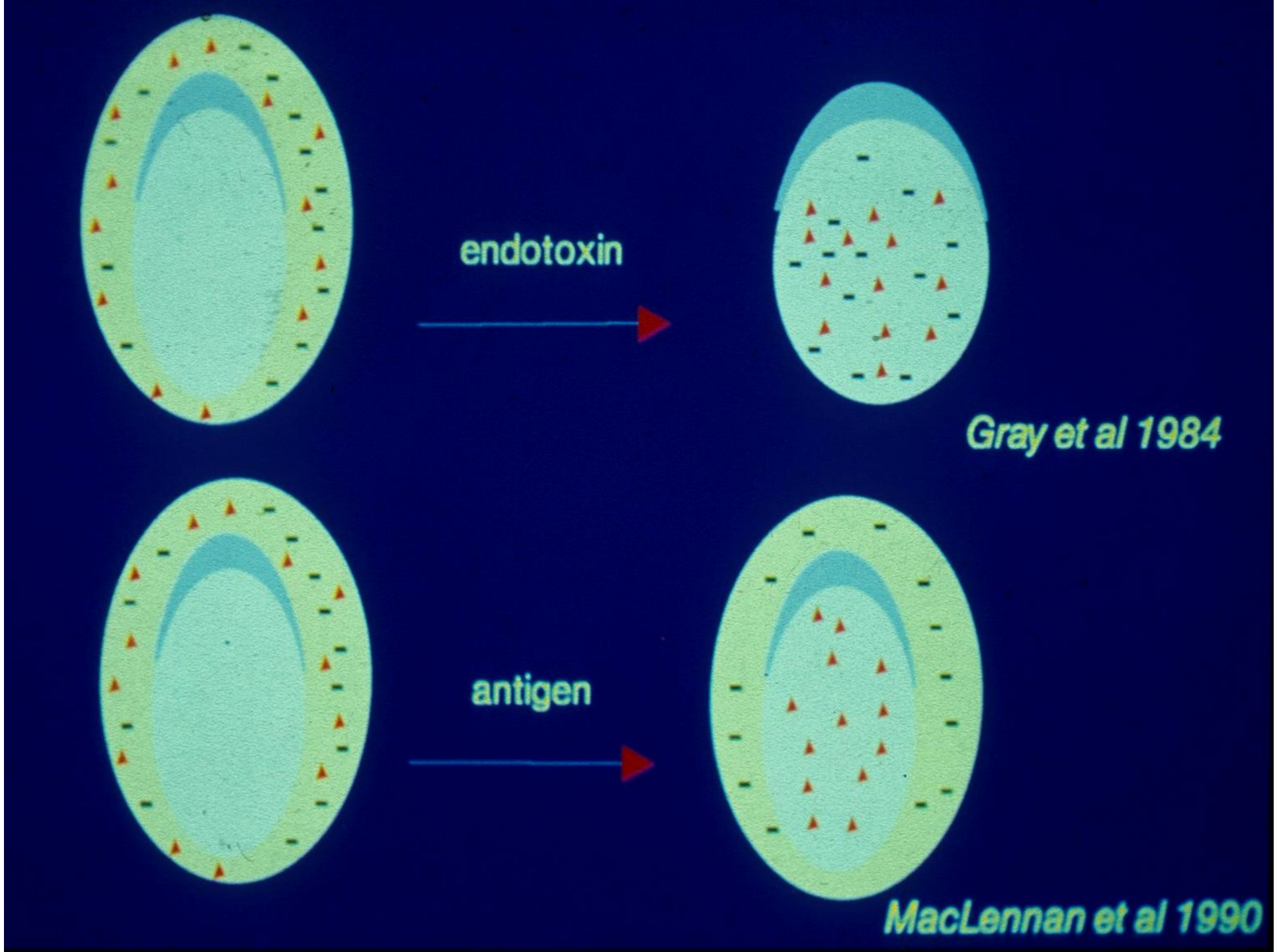







endotoxin
Gray et al 1984
antigen
MacLennan et al 1990

H pylori Eradication in Gastric Lymphoma

AUTHOR	YEAR	CASES	REGRESSION	%
Wotherspoon *et al*	1993	6	5	83
Roggero *et al*	1995	25	15	60
Beyerdorffer *et al*	1995	33	23	69
Montalban *et al*	1995	4	4	100
Savio *et al*	1996	13	11	85
Neubauer *et al*	1998	120	95	79
Steinbach *et al*	1999	18	14	76
Nakamura *et al*	2001	41	30	72
Total		260	197	76

Antibiotic Treatment of Gastric Lymphoma

- Removes *H pylori* specific T-cell growth stimulus
- Results in sustained endoscopic and histological regression of lymphoma
- Lymphoma cells may remain dormant
  - Ig_H PCR still positive
- Relapse of *H pylori* infection may cause re-growth of lymphoma
- In 75% of cases suppresses, but does not always ablate the neoplastic clone

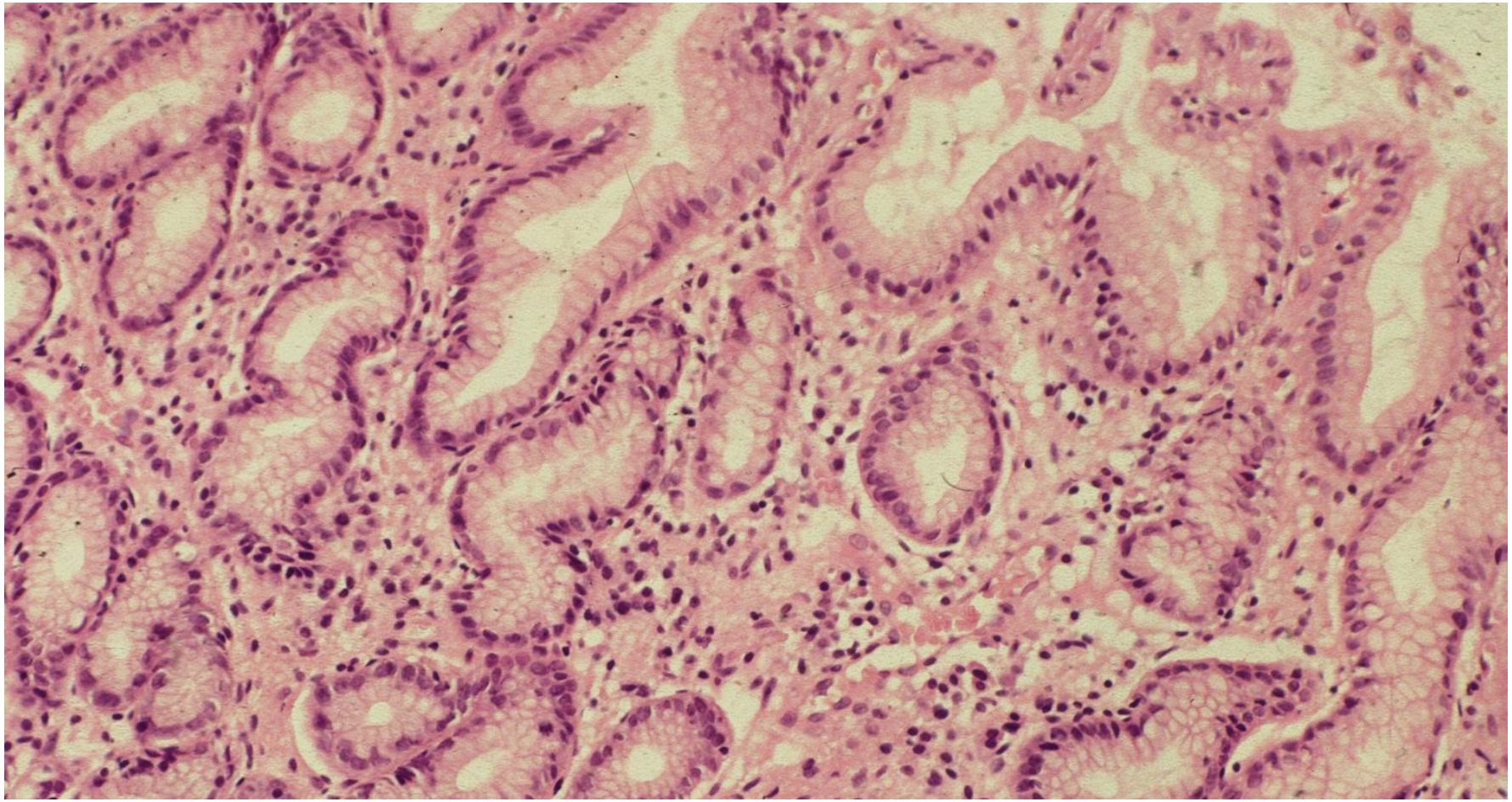
Follow-up histological scoring system for treated gastric MALT lymphoma

Score		Lymphoid infiltrate	LEL	Stromal changes
CR	**Complete Histological remission**	absent **or** scattered plasma cells and small lymphoid cells in the LP	absent	normal **or** empty LP **and/or** fibrosis
pMRD	**Probable minimal residual disease**	aggregates of lymphoid cells **or** lymphoid nodules in the LP/MM and/or SM *	absent	empty LP **and/or** fibrosis
RD	**Responding disease**	dense diffuse or nodular	focal LEL **or** absent	focal empty LP **and/or** fibrosis
NC	**No change**	dense diffuse or nodular	present " maybe absent "	no changes

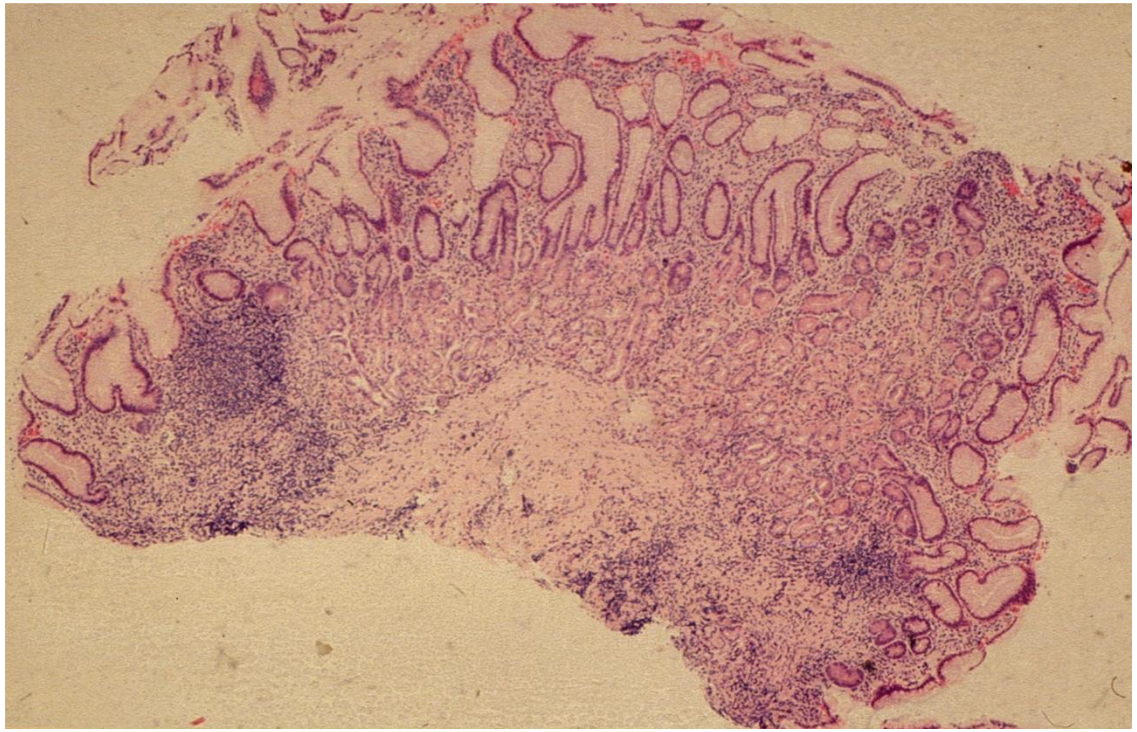
²Abbreviations : MM=muscularis mucosa ; LP= lamina propria ; SM= submucosa
LEL=lymphoepithelial lesions

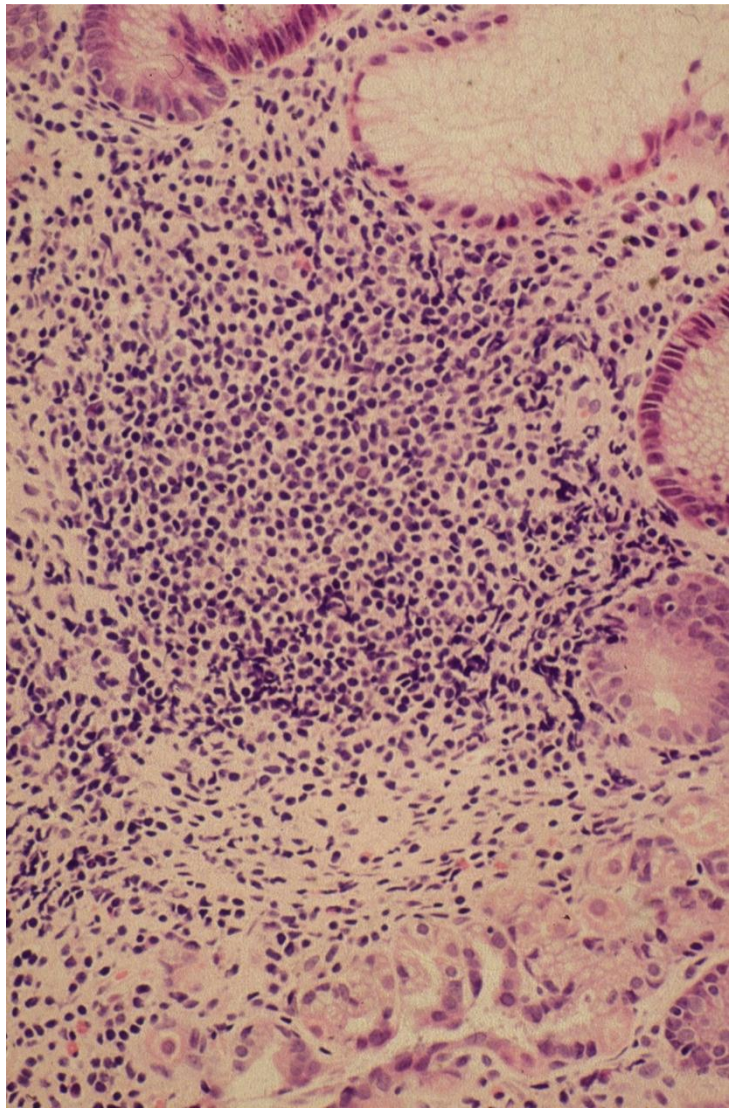
*this category includes cases with minimal residual disease and cases with minimal lymphoid infiltrate where residual disease cannot be excluded.

Complete histological remission

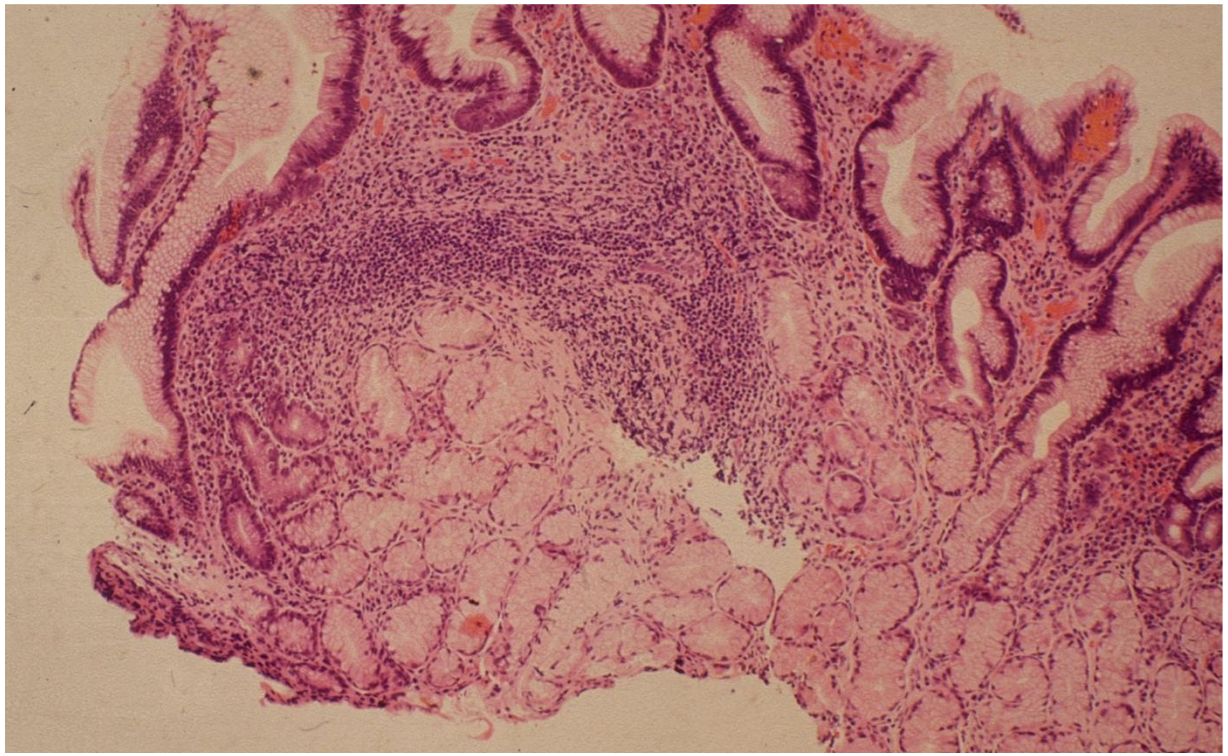


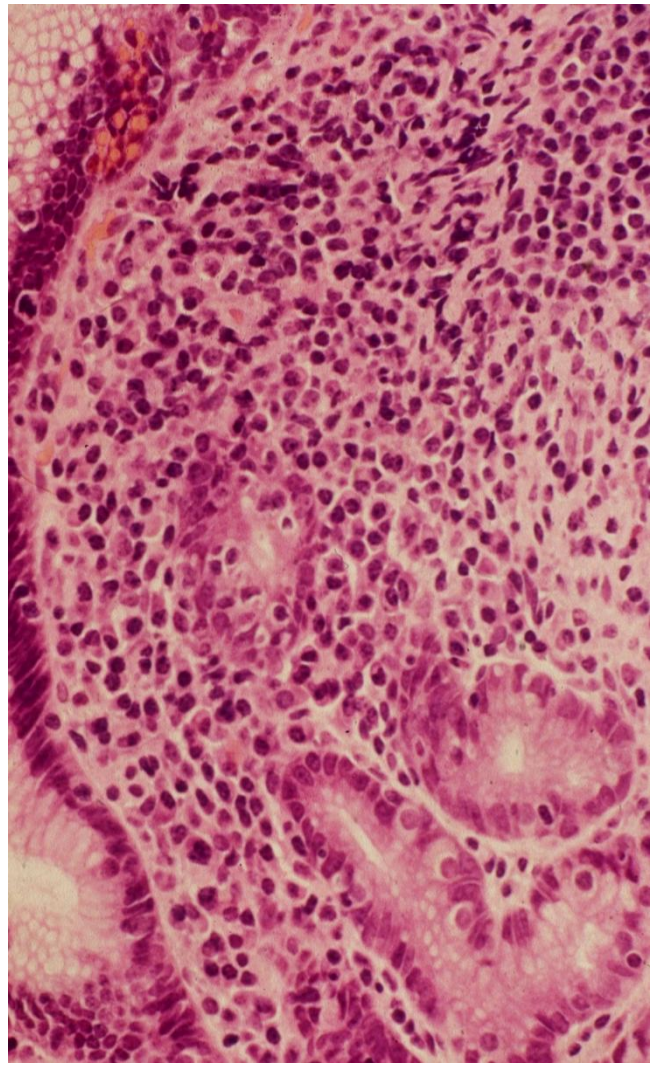
Probable minimal residual disease



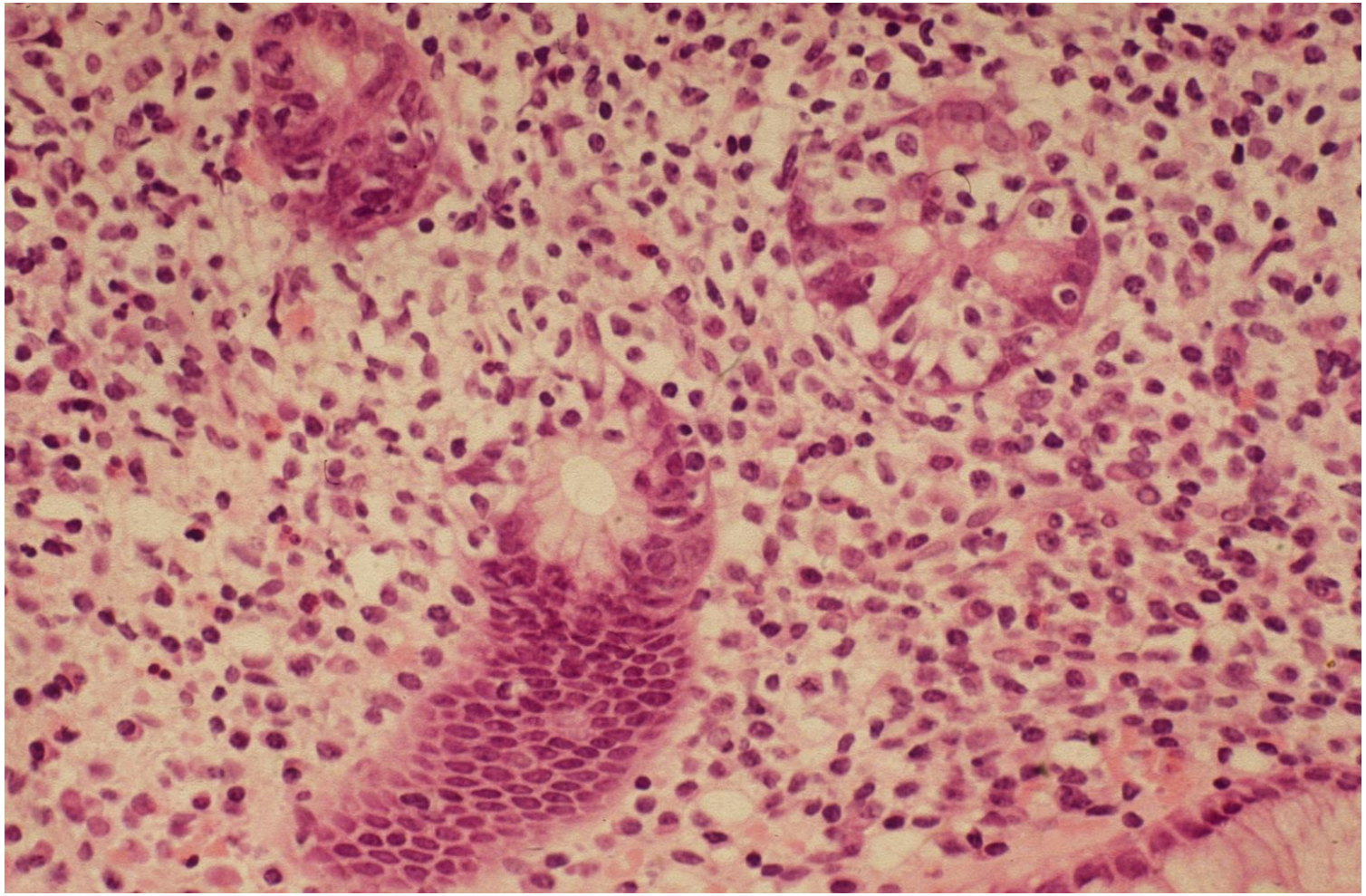


Responding disease





No change



Monoclonality after response to Hp eradication therapy

19 patients with long follow-up monoclonal at diagnosis

3 patterns of clonality in follow-up biopsies

Pattern 1	stable polyclonal	4 (21%)
Pattern 2	maintained/sustained monoclonality	8 (58%)
Pattern 3	occasional monoclonality	4 (21%)

1 relapse – pattern 2

Montalban et al 2005

Where are the clonal lymphoid cells?

- Microdissection of follow up samples from 3 patients
- Basal lymphoid aggregates

  All 3 cases showed clonal (PCR detected) populations with PCR bands of identical size to original lymphoma
- Upper mucosa

  1/2 patients had a clonal population with PCR band of similar size to original lymphoma but sequence analysis showed clones were unrelated

Thiede et al 2001

Fate of residual microscopic disease

7 patients with endoscopic CR but with residual microscopic disease at 12m
Refused further therapy

	t(11;18)	JH PCR	FU
43F	+	+	30
469M	+	+	44
46M	NA	NA	34
57M	-	-	37
65M	NA	NA	34
62F	+→ -	+	20
49M	+	+	22

No relapse No transfromation

Fischbach et al 2002

Predictive value of EUS for regression of gastric low grade and high grade MALT lymphoma after eradication of H pylori
Nakamura et al 2001

	No	**CR**
mucosa/submucosa	28	26 (93%)
deep submucosa	5	1 (20%)
musc.propria	5	2 (40%)
serosa	3	0
Regional LN	5	3

t(11:18) and response of gastric MALT lymphoma to Helicobacter eradication Liu et al 2001

22 cases

	No	t(11:18)
Hp responsive	10	0
No response	12	9

Predictors of response to Helicobacter eradication

- Depth of invasion of gastric wall
- Helicobacter status at diagnosis
- Presence/absence of large cell component
- Immunocytochemistry
  - nuclear bcl-10
  - nuclear NF-kB
- Molecular abnormalities
  - API2/MALT-1 fusion
  - t(1;14)
  - Trisomy 3

Lancet. 1991 Nov 9;338(8776):1175-6.

Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma.

Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG.

Author information

Abstract

Although lymphoid tissue is absent in normal gastric mucosa, primary lymphomas arise in the stomach and most of these recapitulate the features of mucosa-associated lymphoid tissue (MALT). Gastric lymphoid tissue is known to be acquired in response to local infection by Helicobacter pylori, and we have confirmed this in 450 patients with H pylori-associated gastritis of whom 125 showed mucosal lymphoid follicles. In 8 patients, B lymphocytes infiltrated epithelium, which is a feature characteristic of MALT. We also examined 110 cases of gastric MALT lymphoma and found H pylori infection in 101 of these (92%). We conclude that gastric MALT is acquired in H pylori infection and that this provides the necessary background in which MALT lymphoma might develop.

1991
92% prevalence
of Hp in gastric MALT lymphoma

Prevalence of Hp infection in patients with gastric MALT lymphoma: review of the literature

Author	Year of publication	N#	Prevalence of Hp (%)	Diagnostic method
Luminari et al[24]	2009	51	61 (1997-2002) 17 (2002-2007)	HP
Gisbert et al[25]	2006	37	46	HP, RUT, cBT,
Nakamura et al[18]	2005	96	93	HP, RUT, cBT, S, CT
Lee et al [32]	2004	53	90	HP, RUT
Yeh et al33	2003	20	85	HP, RUT, cBT
Lehours et al[34]	2003	56	71	HP, CT, S
Ruskone et al[35]	2001	44	77	HP, CT, S
Delchier et al[36]	2001	53	85	S
Hiyama et al [37]	2001	53	92	HP
Cuttner et al [38]	2001	12	67	S
Ben rejeb et al[39]	2000	65	63	HP
Arista-nasr et al[40]	2000	54	57	HP
Fischbach et al [19]	2000	35	100	S
Konturek et al[41]	2000	20	90	S, cBT
Ohashi et al [42]	2000	23	61	HP, RUT, CT
Steinbach et al[43]	1999	34	82	HP, RUT, S
Eck et al[44]	1999	60	98	HP, S
Chang et al[45]	1999	53	75	HP
Dogusoy et al[46]	1999	32	72	HP
Bouzourene et al[47]	1999	31	58	HP
Vallina et al[48]	1999	16	69	HP
H Yi et al[49]	1997	39	87	HP
Jonkers et al[50]	1997	52	69	HP
Oberhuber et al[51]	1997	89	84	HP
Pavlick et al[52]	1997	16	69	HP
Eck et al[20]	1997	68	99	S
Xu et al[21]	1997	53	55	HP
Gisbertz et al[22]	1997	52	62	HP
Nakamura et al[17]	1997	198	63	HP
Chiang et al[53]	1996	19	92	HP, S
Herrera et al[54]	1996	27	85	HP
Cammarota et al[55]	1996	39	87	HP, RUT, CT
Miettinen et al[56]	1995	22	59	HP
Karat et al [23]	1995	12	50	HP, RUT, S
Calvert et al[15]	1995	12	42	HP
Muller et al[57]	1995	45	80	HP
Parsonnet et al[58]	1994	33	85	S
Eidt et al[16]	1994	121	100	HP
Fagioli et al[59]	1994	27	74	HP
Wotherspoon et al[4]	1991	110	92	HP

HP: histopathology; RUT: rapid urease test; cBT: C-urea breath test; CT: culture; S: stool

Hp infection in GML: a re-evaluation
Results

Wotherspoon et al, 1991:	92% prevalence
1996-2004	60.6% (n:37/61)
2005-2013	32.4% (n:12/37)

Reduction of 64.8%

Hp infection in GML: a re-evaluation
Analysis

- Prevalence reduction. Why?
  - Hp infection in the general population:
    - Reduced Hp acquisition rates (children)

    And/ or

    - Deliberate Hp eradication (other forms of diagnosis → before biopsy)

    And/ or

    - Unintentional eradication (widespread use of antibiotics and over the counter acid suppressing medications)

Helicobacter eradication in Hp negative gastric MALT lymphoma

- 57 patients (Korea)

- 14/57 (25%) Hp negative
  - At least 2 of histology, urea breath test, rapid urease, serology

- 48 patients had eradication therapy
  - 31/39 (79%) Hp+ CR
  - 5/9 (56%) Hp- CR

Ryu et al Gut and Liver 2014

Why is eradication successful in Hp negative patients

- Other organisms
  - Metronidazole more effective than Amoxicillin (Raderer Gut 2006 – 5/6 CR)

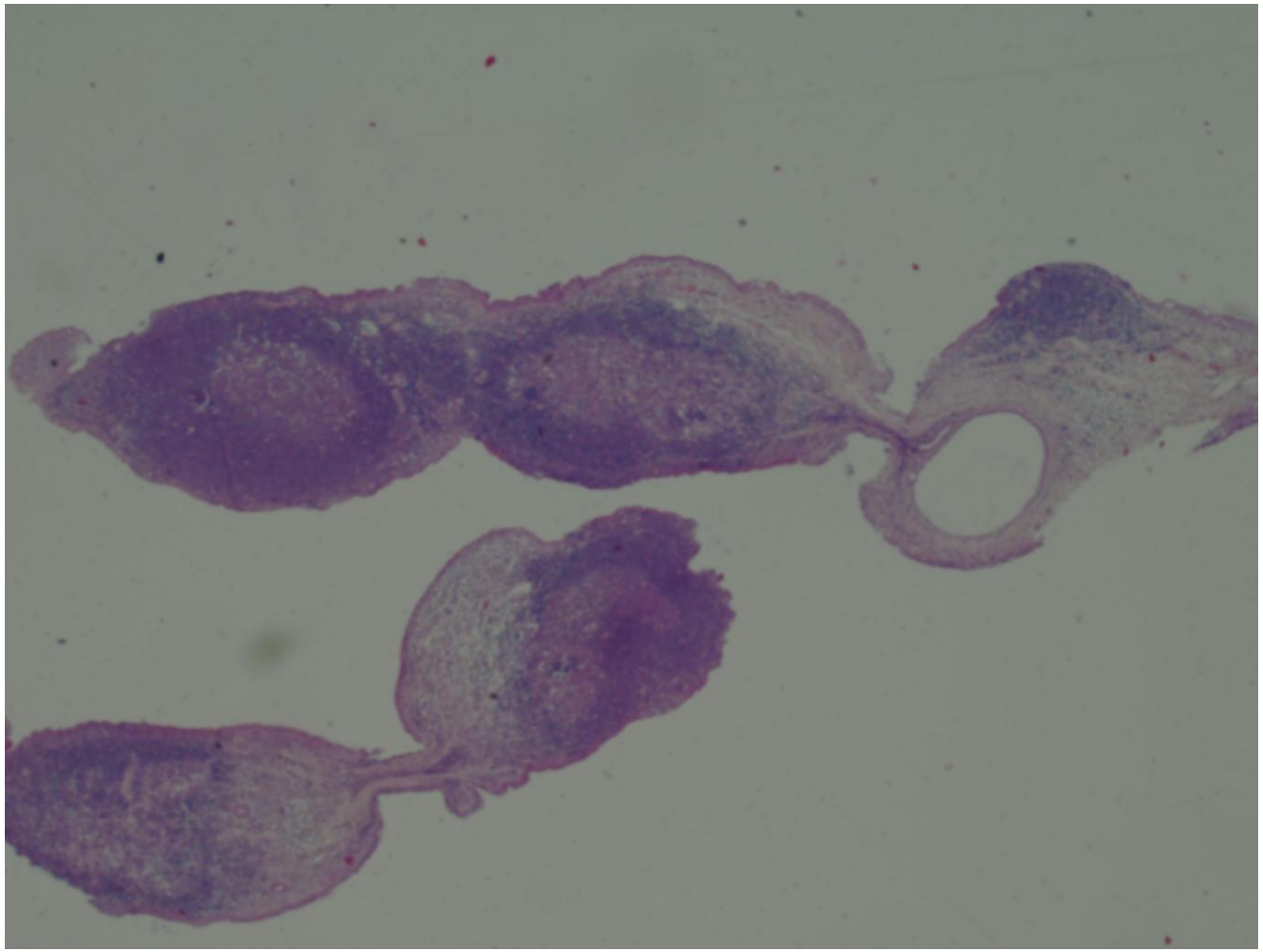
Non-Helicobacter pylori Helicobacter

- Zoonotic gram negative bacteria
  - H suis
  - H felis
  - H bizzozeronii
  - H salomonis
  - H heilmanii
- Inhabit stomachs of animals incl. pigs, cats and dogs
- Spread by contact with animals or eating meat from pigs
- Prevalence in humans 0.1-6.2%
  - Europe lower than Asia (except Japan)
  - 12% in China (Liu et al Helicobacter 2015)
    - All also Hp positive

Why is eradication successful in Hp negative patients

- Other organisms
  - Metronidazole more effective than Amoxicillin (Raderer Gut 2006 – 5/6 CR)

- Clarithromycin
  - Immunomodulatory and antineoplastic properties



Acquired MALT in 31% unselected adults

CHLAMYDIA PSITTACI AND OCULAR ADNEXAL MALT LYMPHOMA

Rosado et al 2006	US	0/49
Ponzoni et al 2008	Italy	24/33
Zhang et al 2010	China	0/38
Carugi et al 1010	Italy	4/22
	Kenya	0/9

CHLAMYDIA PSITTACI ERADICATION IN OCULAR ADNEXAL LYMPHOMA
Ferreri et al JCO 2012

CR	6/34
PR	16/34
Stable disease	11/34
PD	1/34

12/14 eradicated – objective response

7/15 not eradicated – objective response

In patients with CR no relapse after treatment (FU 36-60m)

Pulmonary MALT lymphoma and Achromobacter (Alcaligenes) Xylosoxidans

- Gram negative betaproteobacterium
- Low virulence
- High resistence to antibiotics

Initial study

- 16S rRNA gene based approach
- 6/9 cases positive in initial study

Follow up study – 6 European countries (FFPE)

- 57/124 (46%) MALT lymphoma samples
- 15/82 (18%) Control lung tissue (p=0.004)

Adam et al Pathologe 2008; BJH 2014

ASSOCIATION BETWEEN BORRELIA INFECTION AND CUTANEOUS B CELL LYMPHOMA

Aberer et al 2011	Austria	MZL	1/1 (100%)
Goodlad et al 2000	Scotland (highland)	FCL	1/5 (20%)
		DLBCL	1/3 (33%)
		MZL	5/12 (42%)
Cerroni et al 1997	Austria	FCL	3/20 (15%)
		DLBCL	1/6 (17%)
		MZL	2/20 (10%)
		LpcL	3/4 (75%)

CUTANEOUS B CELL LYMPHOMA TREATED WITH ANTIBIOTICS

Garbe et al 1991	serol	LG B-NHL; sm/med, cleaved nucl	NR
	serol	LG B-NHL; CB-CC	NR
	serol	LG B-NHL; Sm, cleaved nucl	NR
	serol	LG B-NHL; med, cleaved nucl	NR
Kutting et al 1997	serol/cult/pcr	MZL	CR
	serol/cult	FCL	NR
Roggero et al 2000	serol/pcr	MZL	CR
Grange et al 2003	serol/pcr	FCL	CR
	serol/pcr	DLBCL	CR
de la Fouchardiere et al 2003	pcr	MZL	CR
Aberer et al 2011	serol/pcr	MZL	CR

Precursors of MALT lymphoma

Stomach	*Helicobacter pylori*
Small intestine (IPSID)	*Campylobacter jejuni*
Conjunctiva/orbit	*Chlamydia psitticae*
Skin	*Borrelia burgdorferi*
Lung	*Achromobacter xylosoxidans*
?many	Hepatitis C
Thyroid	Hashimoto’s thyroiditis
Salivary gland	Sjogren’s disease

Bacteria and EMZL

Table 1. Evidence of for linking a specific microorganism to MALT lymphoma of different sites

Koch's postulates for linking a specific microorganism to a disease (1882)*	Gastric MALT lymphoma	IPSID	Cutaneous MALT lymphoma	Ocular adnexal MALT lymphoma
	H. pylori	*C. jejuni*	*B. burgdorferi*	*C. psittaci*
The organism is found in the lesion of the disease.	~ every case	Some cases	Variable	Variable
The organism can be isolated and grown *in vitro*.	Yes	not yet	not yet	YES
Inoculation of the organism causes lesions in healthy susceptible animals	Yes	unknown	unknown	unknown
The organism can be recovered from the experimental animal.	Yes	unknown	unknown	unknown
	Cure disease following *H. pylori* eradication in the majority of cases.	unknown	Cure disease following *B. burgdorferi* eradication in some cases	Cure disease following *C. psittaci* eradication in some cases.

Modified from Du M-Q. J Clin Exp Hematopathol 2007

Immunoproliferative Small Intestinal Disease (IPSID)

- Distribution
  - Middle East
  - North and South Africa
  - Far East
- Age
  - Mean 25-30 (range 10-35)

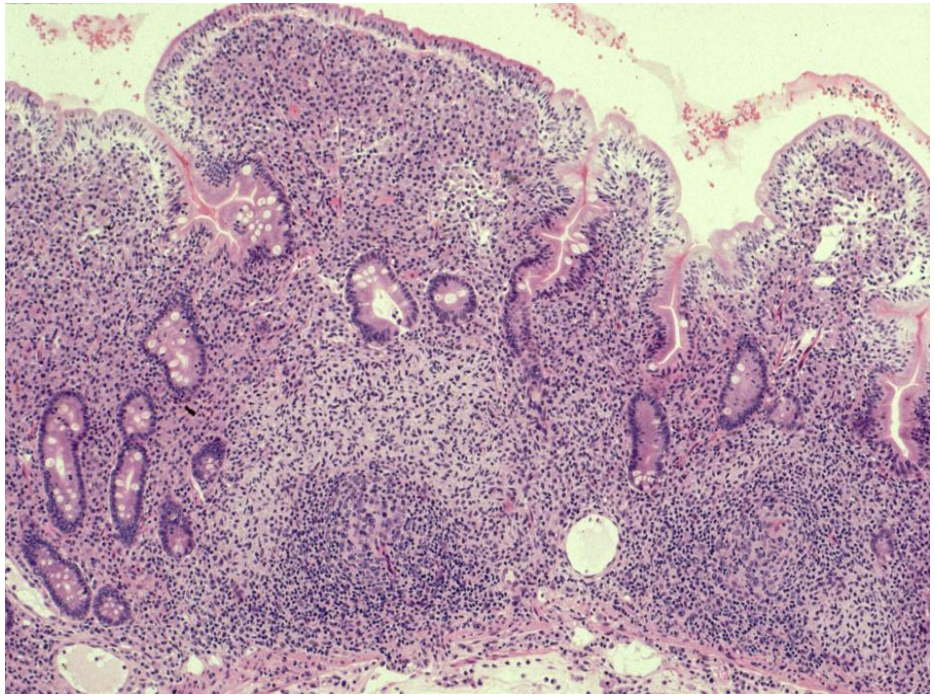
Immunoproliferative Small Intestinal Disease (IPSID)

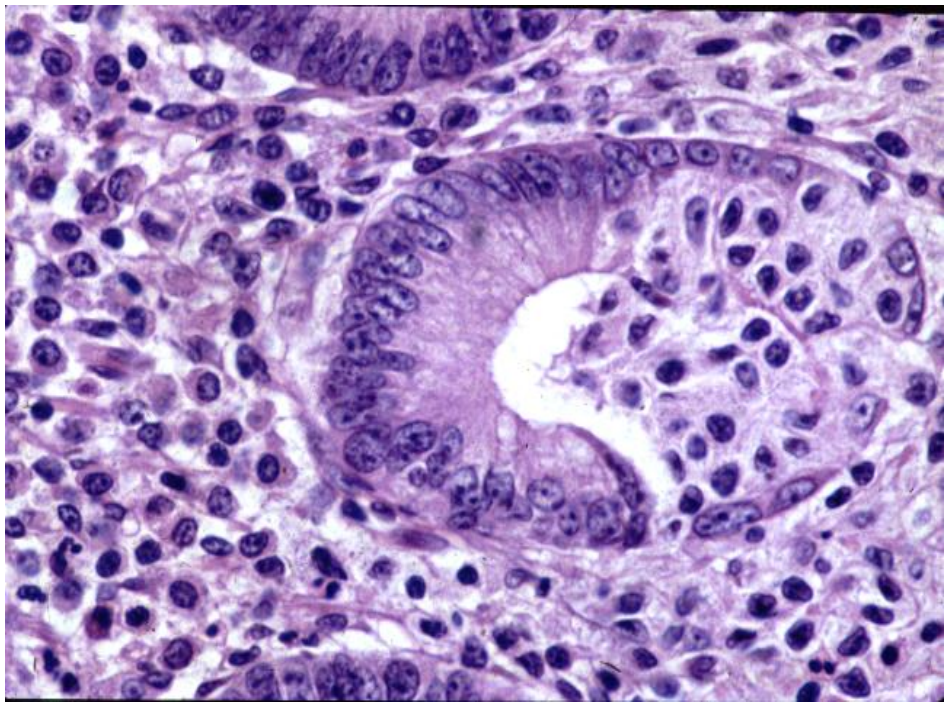
- Symptoms
  - Intermittent diarrhoea
  - Colicky abdominal pain
  - Malabsorption
- Endoscopy
  - $2^{nd}/3^{rd}$ and 4^{th} part of Duodenum and upper jejunum
  - Thickening
  - Erythema
  - Nodularity of mucosal folds

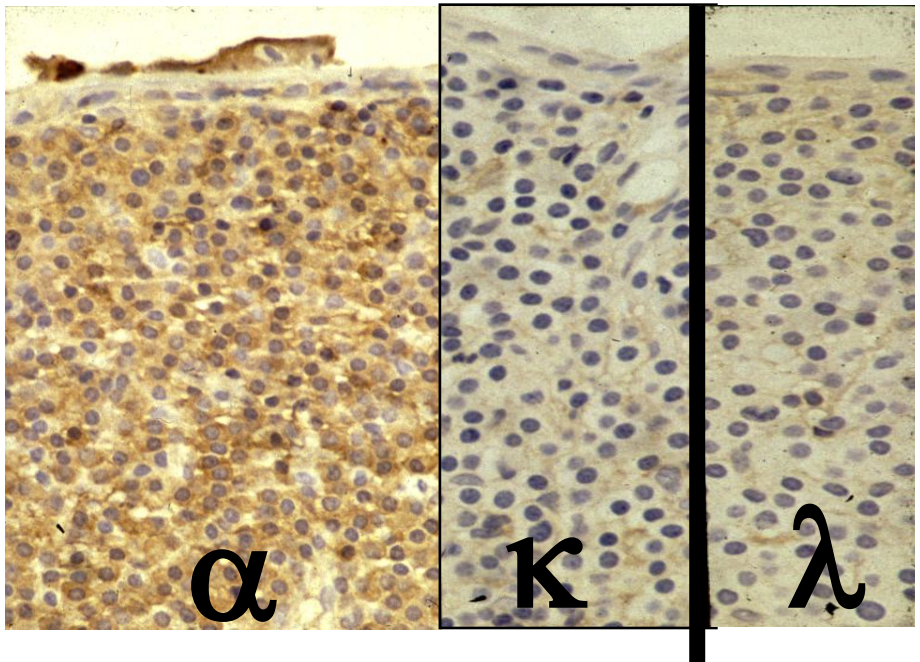
Immunoproliferative Small Intestinal Disease (IPSID)

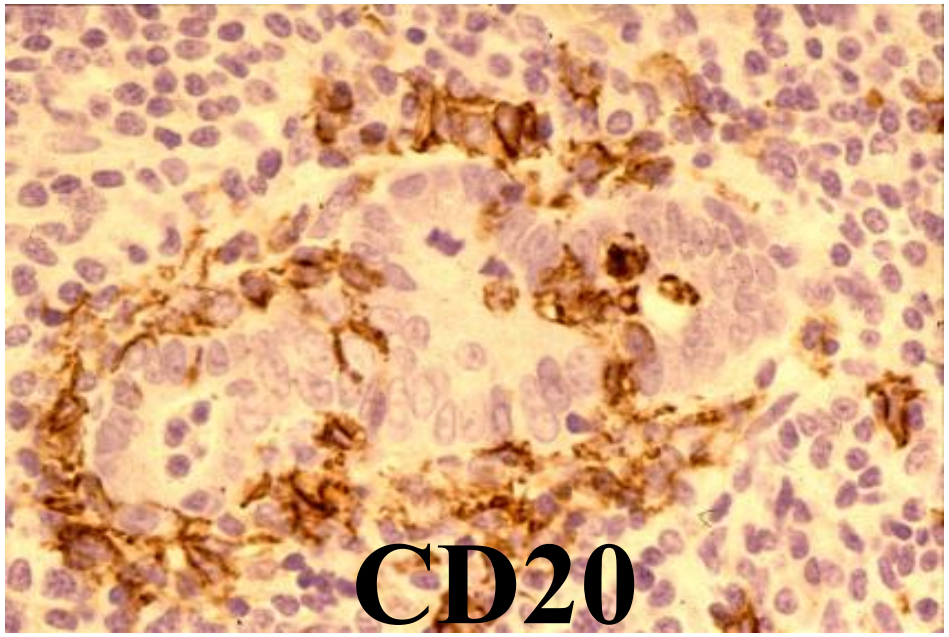
Histology

- Mucosal infiltration by centrocyte-like cells (may be scanty)
- Plasmacytosis of lamina propria
- Associated with α heavy chain in serum (α heavy chain disease)
- Tumour cells produce abnormal Ig α chain but no light chains
- Emergence of pleomorphic immunoblastic lymphoma in a minority






α
κ
λ


CD20

IPSID

Immunophenotype and molecular genetics

- CD20+ (CCL), CD79a+, CD138+ (plasma cells)
- Ig alpha+
- Kappa and Lambda -, CD3-, CD10-, Bcl-6-, CD5-, Cyclin D1-
- CD21 highlights FDC meshwork
- BIRC3::MALT1 negative

Campylobacter and B-cell Lymphoma

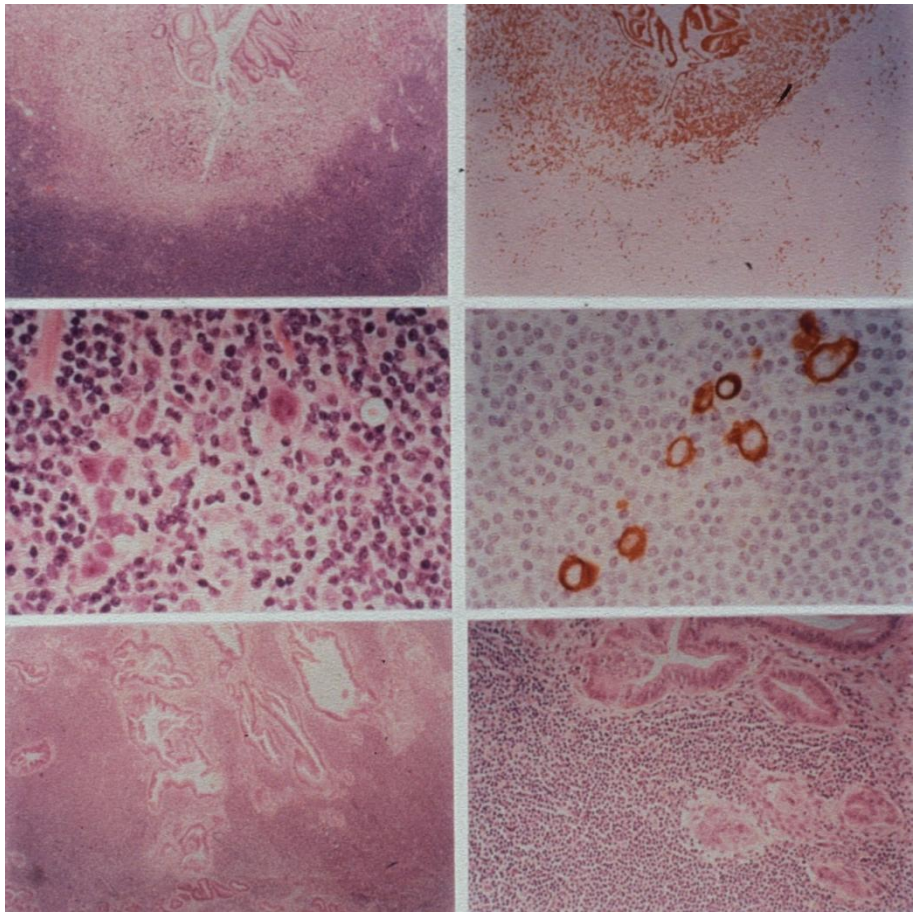
- Campylobacter infection may persist for > 1 year
- Campylobacter is a potent inducer of B-cell activating factor of the TNF family (BAFF) in human dendritic cells
- BAFF
  - Prolongs B-cell survival
  - Increased expression in tumoral B-cells
  - Increased serum levels in patients with B-cell lymphoma

Mackay et al Ann Rev Immunol 2003

Regression of IPSID Following Broad Spectrum Antibiotics

Smith WJ et al (1987)	**2 cases**
O'Keefe et al (1988)	**1 case**
Ben-Ayed et al (1989)	**2 cases**
Matsumoto et al (1996)	**1 case**
Fischbach et al (1997)	**1 case**
Akbulut et al (1997)	**3 cases**
Lecuit et al (2004)	**1 case**

Gastric MALT lymphoma and adenocarcinoma



EXTRANODAL MARGINAL ZONE LYMPHOMA Differential Diagnosis

- Lymphoma vs Reactive

IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Morphology
- Immunophenotype
- Molecular (clonality) studies

IS IT LYMPHOMA?

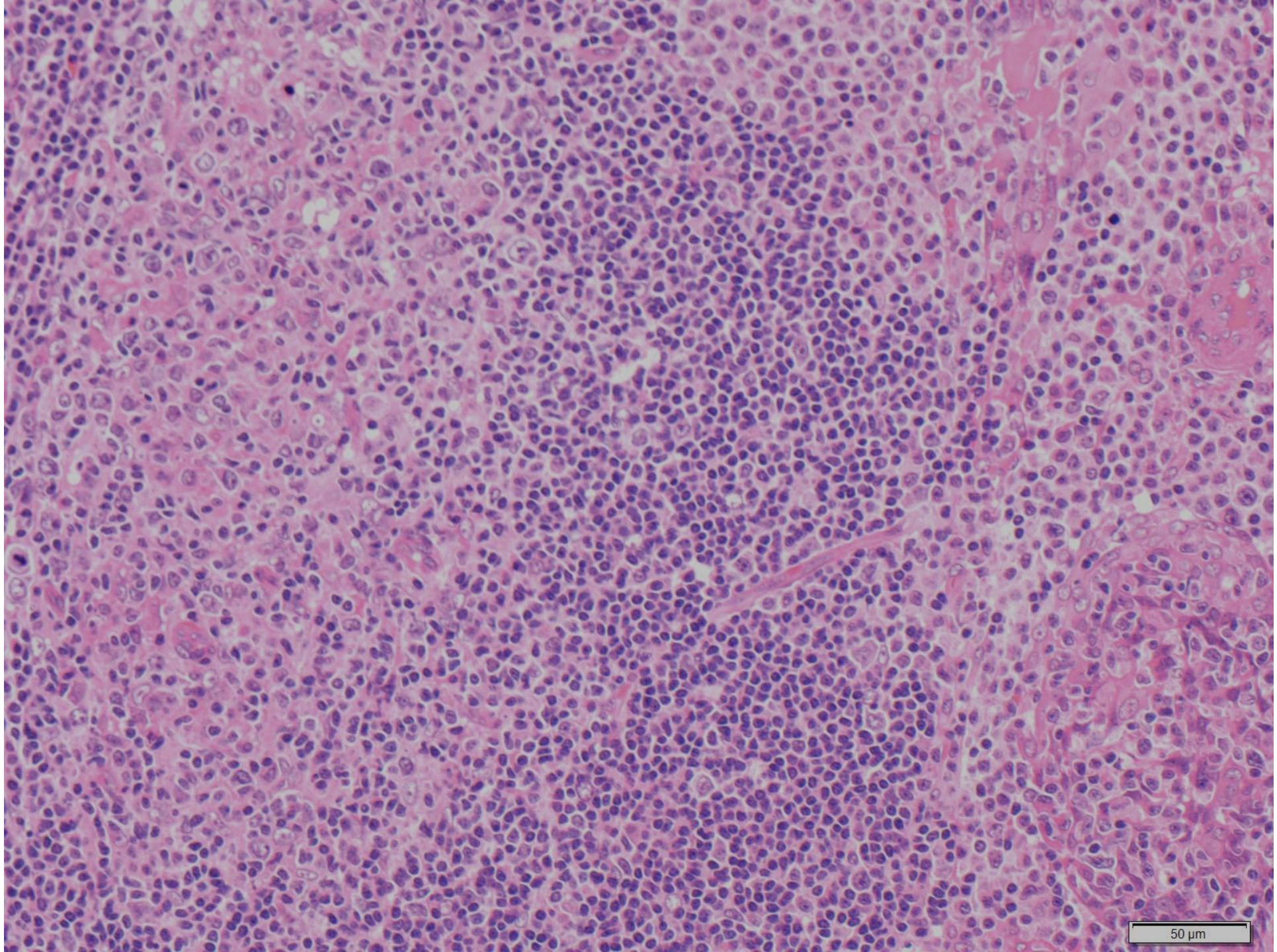
ACQUIRED vs NEOPLASTIC MALT

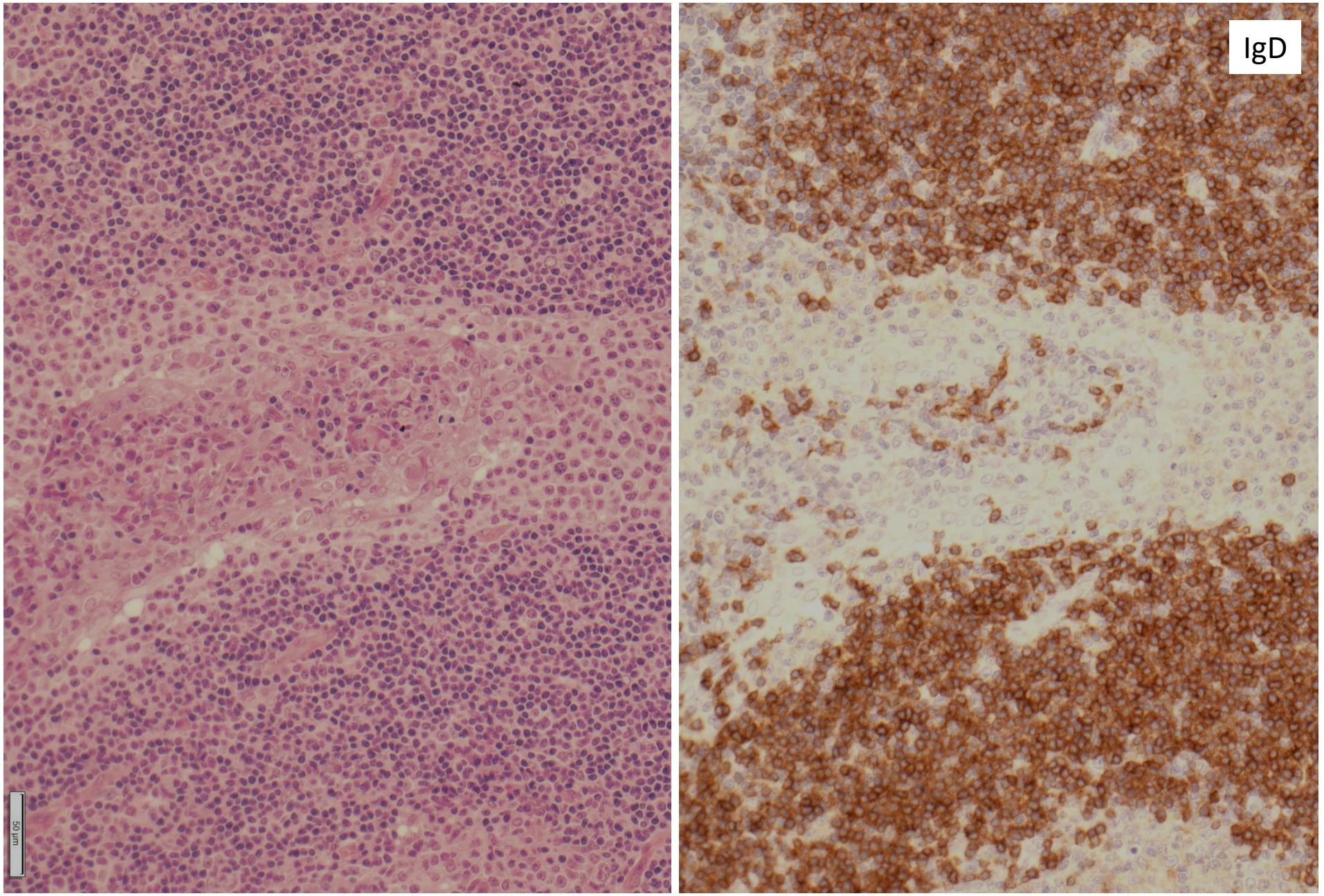
- Morphology

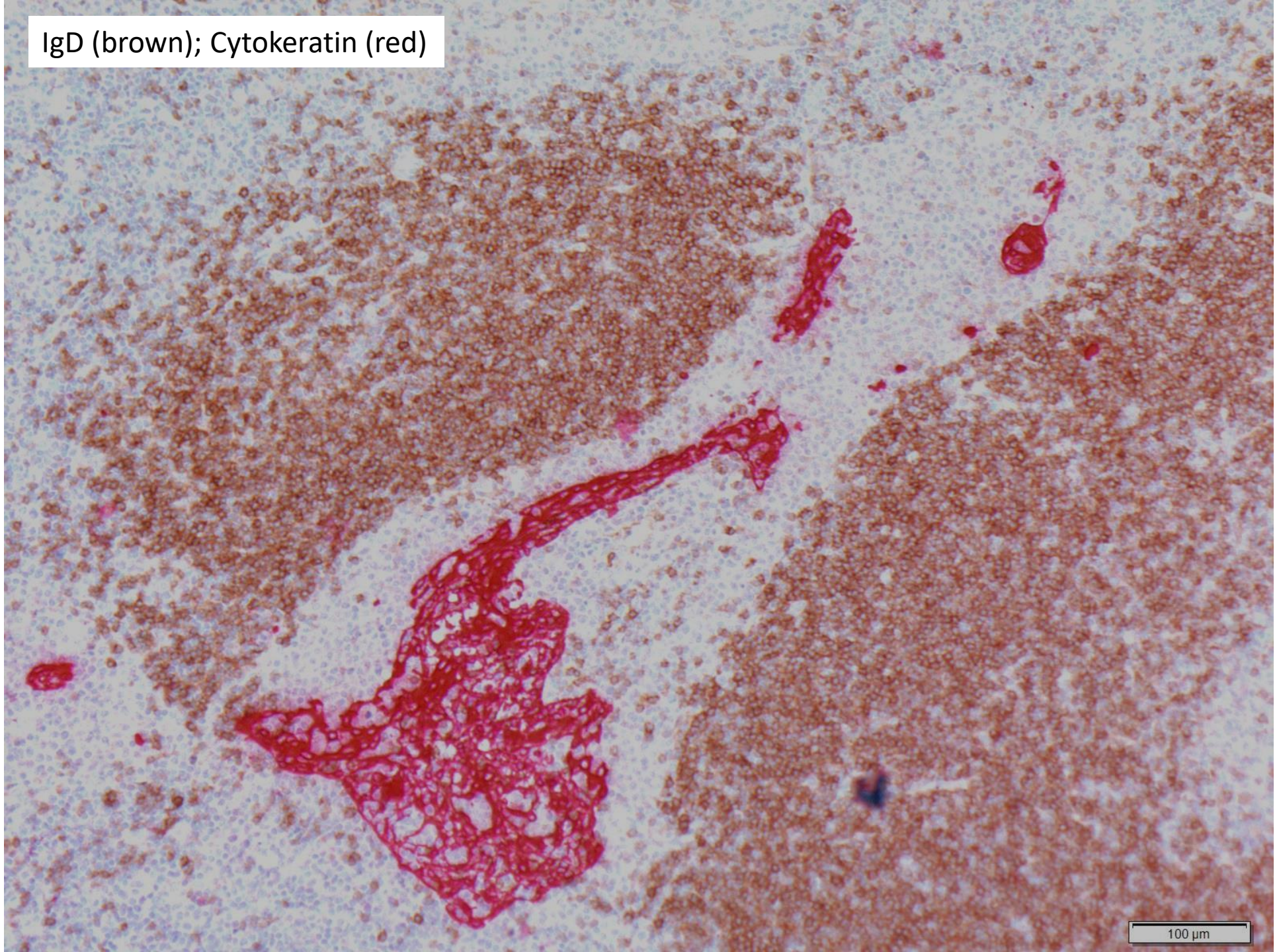
IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

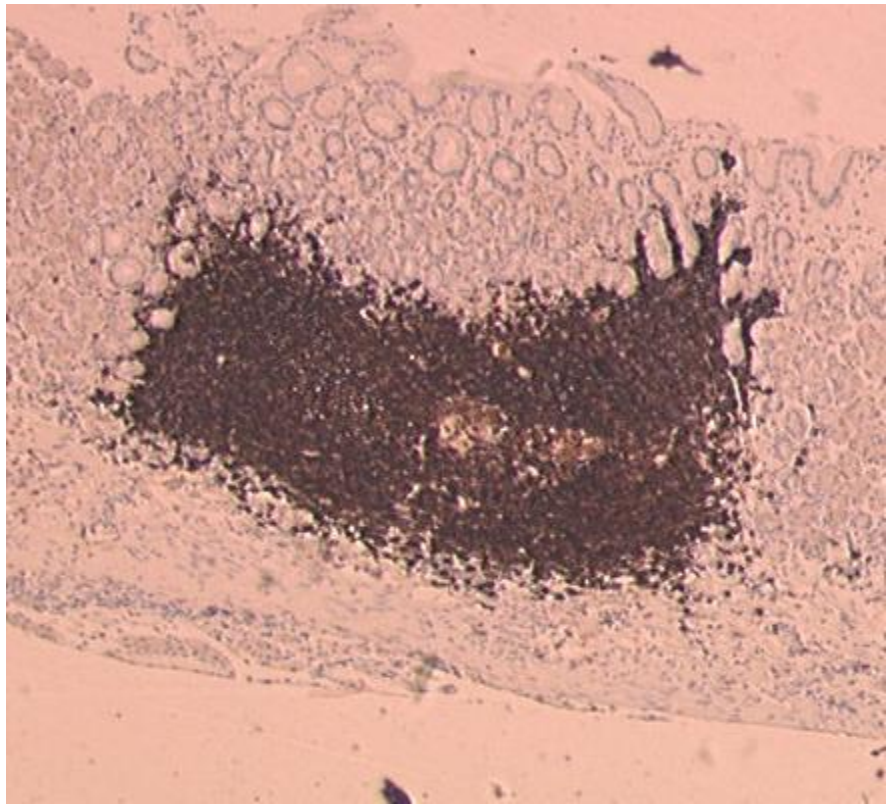
- Morphology
  - Early changes

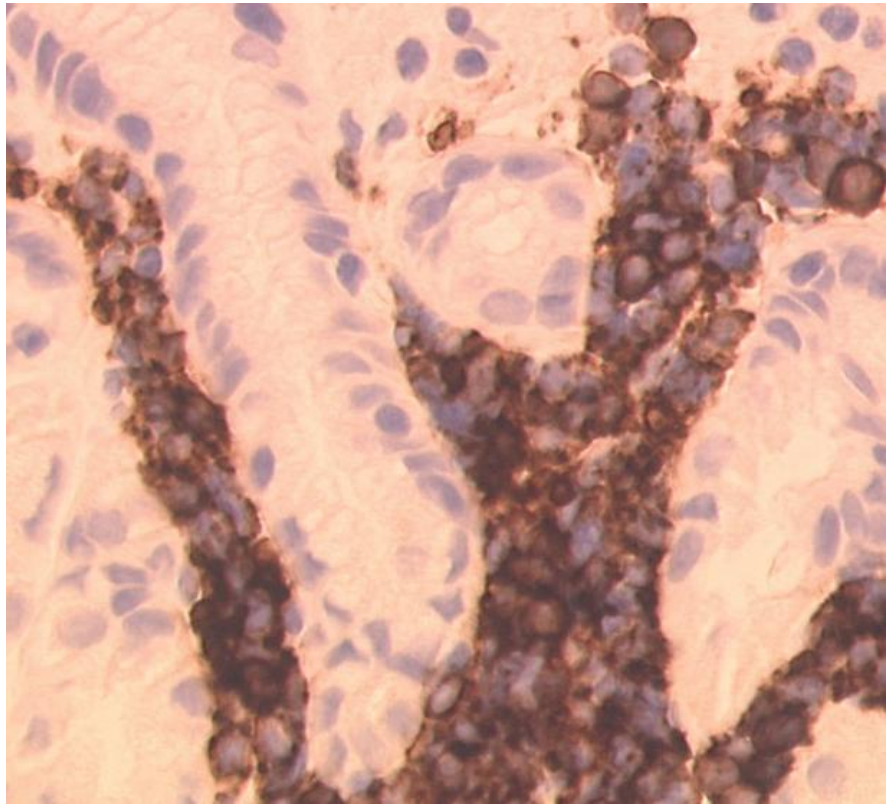

50 µm


50 µm
IgD


IgD (brown); Cytokeratin (red)
100 µm

Histological features associated with early gastric MALT lymphoma

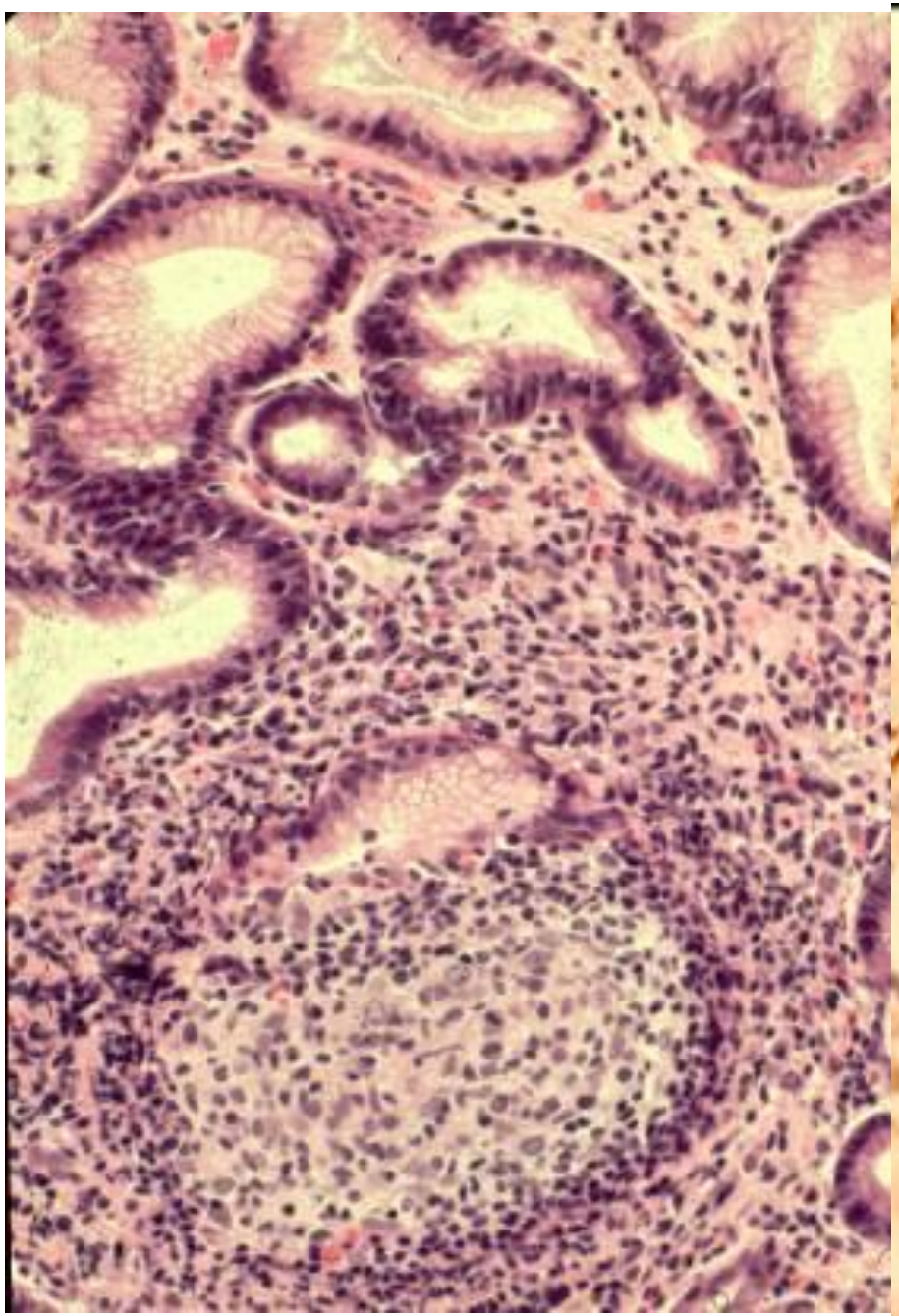


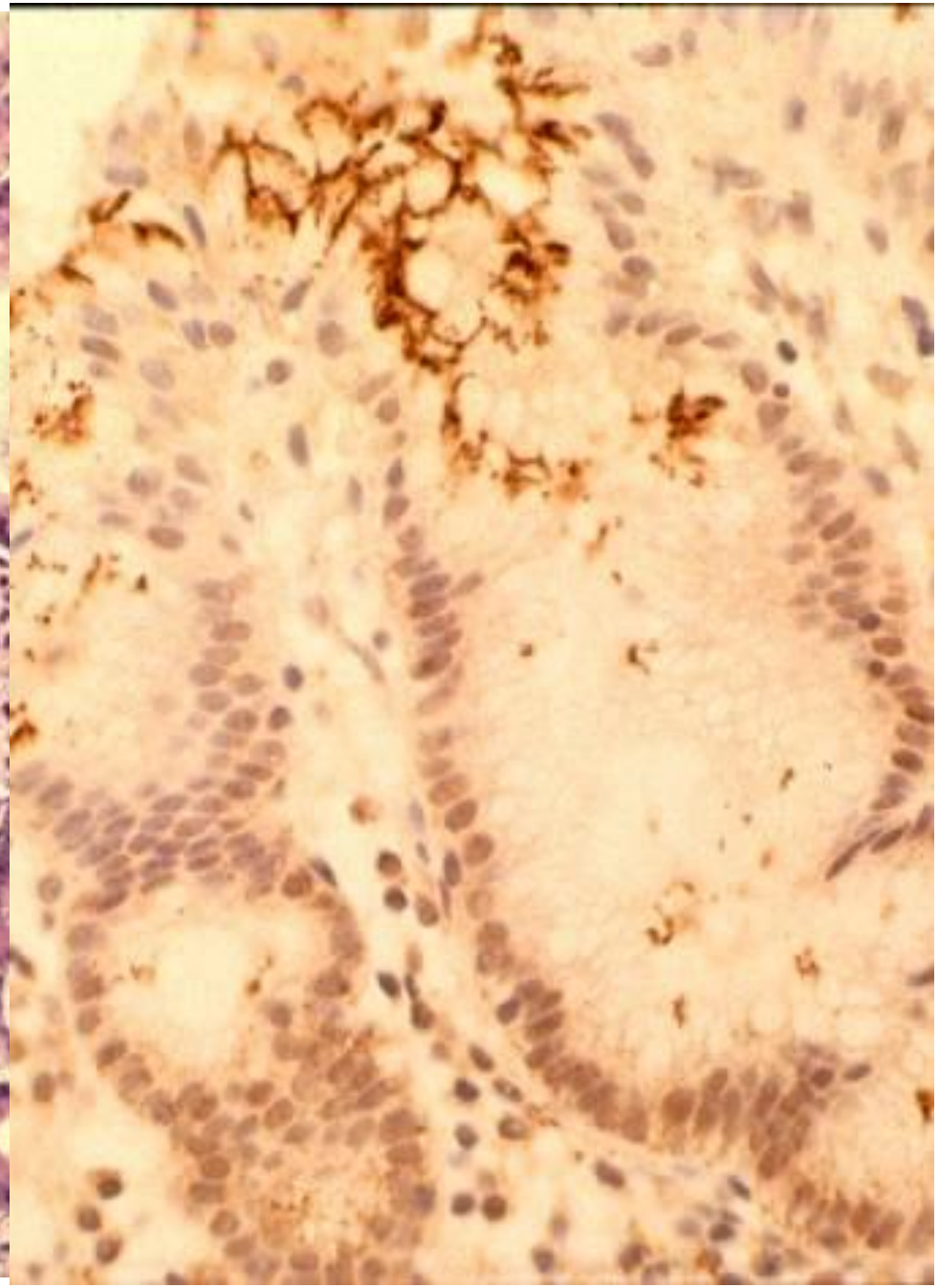


IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Morphology
  - Early infiltration
  - Lymphoepithilum vs lymphoepithelial lesion

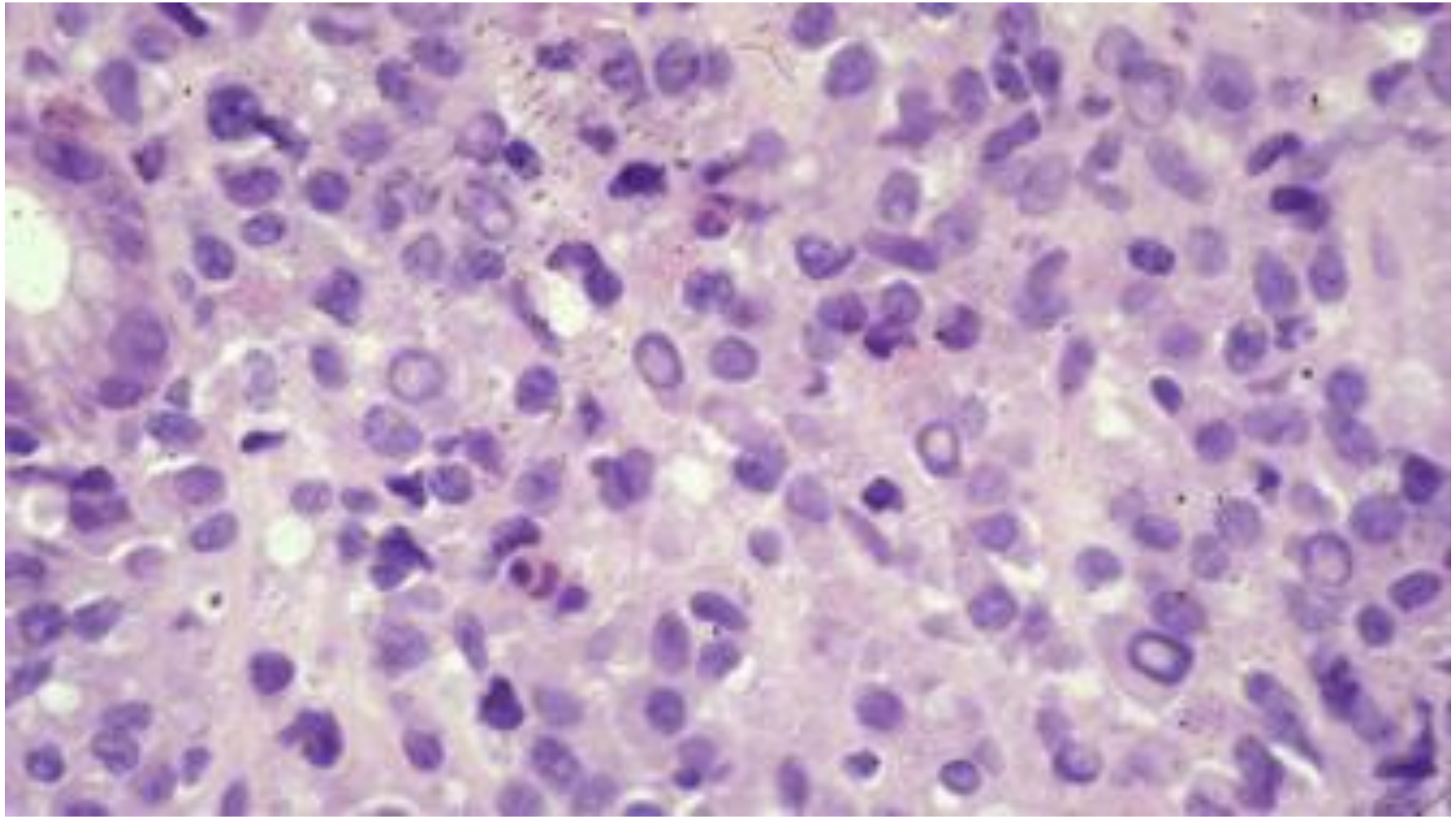




IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Morphology
  - Early infiltration
  - Lymphoepithilum vs lymphoepithelial lesion
  - Dütcher body



Lymphoid Infiltrates in the Stomach
Zukerberg et al Am J Surg Pathol 1990 14; 1087-1099

	LYMPHOMA	GASTRITIS
Prominent LEL	8/24 (33%0	0/58
Dutcher bodies	3/25 (12%	0/58
Moderate cytological atypia (small cleaved cells)	9/25 (36%)	0/58
Dense lymphoid infiltrate	25/25 (100%)	5/58 (9%)
Rare/questionable LEL	11/16 (69%)	17/58 (29%)
Ulceration	12/24 (50%)	5/58 (9%)
Infiltration of muscularis mucosae	20/20 (100%)	20/47 (43%)
Mild cytological atypia	8/16 (50%)	6/58 (10%)
Prominent acute inflammation	2/25 (8%)	27/58 (47%)

Not discriminatory: Germinal centres, crypt abscesses, reactive epithelial atypia

IS IT LYMPHOMA?

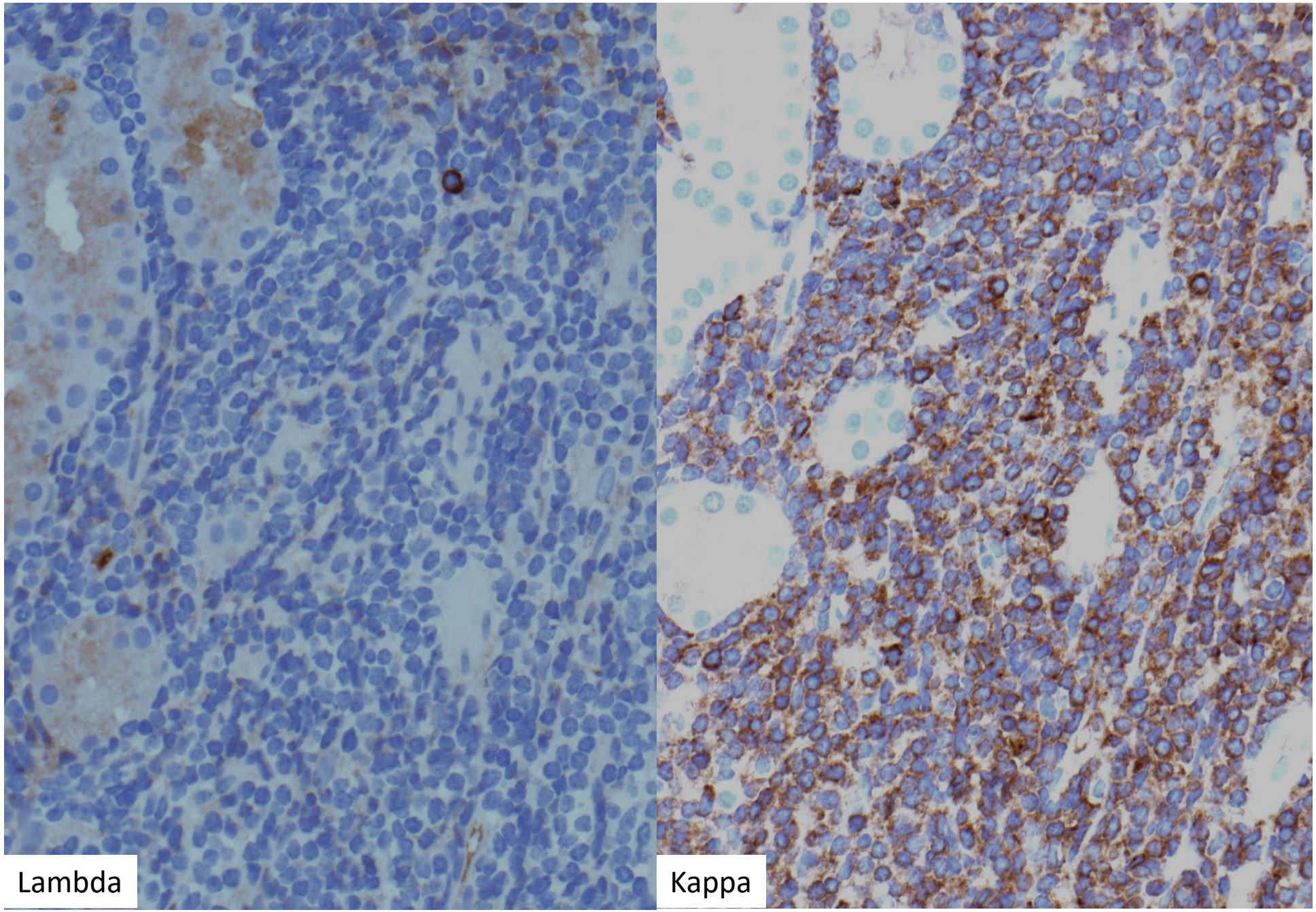
ACQUIRED vs NEOPLASTIC MALT

- Immunophenotype
  - CD43

IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Immunophenotype
  - CD43
  - Immunoglobulin light chain restriction


Lambda
Kappa

IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Immunophenotype
  - CD43
  - CD5
  - Immunoglobulin light chain restriction
    - May be difficult to interpret particularly in small biopsies that are partly crushed
    - Reactive plasma cells in background

IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Molecular (clonality) studies
  - BIOMED-2/Euroclonality IGH FR1-3 and IGK
    - False negative rate <5%
  - IGH alone
    - False negative rate ±15%

Significantly improved PCR-based clonality testing in B-cell malignancies by use of multiple immunoglobulin gene targets. Report of the BIOMED-2 Concerted Action BHM4-CT98-3936

PAS Evans[1], Ch Pott[2], PJTA Groenen[3], G Salles[4], F Davi[5], F Berger[6], JF Garcia[7], JHJM van Krieken[3], S Pals[8], Ph Kluin[9], E Schuuring[9], M Spaargaren[8], E Boone[10], D González[11], B Martinez[12], R Villuendas[7], P Gameiro[13], TC Diss[14], K Mills[15], GJ Morgan[1], GI Carter[16], BJ Milner[17], D Pearson[18], M Hummel[19], W Jung[20], M Ott[21], D Canioni[22], K Beldjord[23], C Bastard[24], MH Delfau-Larue[25], JJM van Dongen[26], TJ Molina[27] and J Cabeçadas[28]

IS IT LYMPHOMA?

ACQUIRED vs NEOPLASTIC MALT

- Molecular (clonality) studies
  - Spurious false positive rate occur
    - Rates vary between laboratories
    - May be related to techniques used

Clonality studies must be interpreted with caution and should only be reported with a supportive histological context

IS IT LYMPHOMA?

ATYPICAL MARGINAL ZONE HYPERPLASIA vs MARGINAL ZONE LYMPHOMA

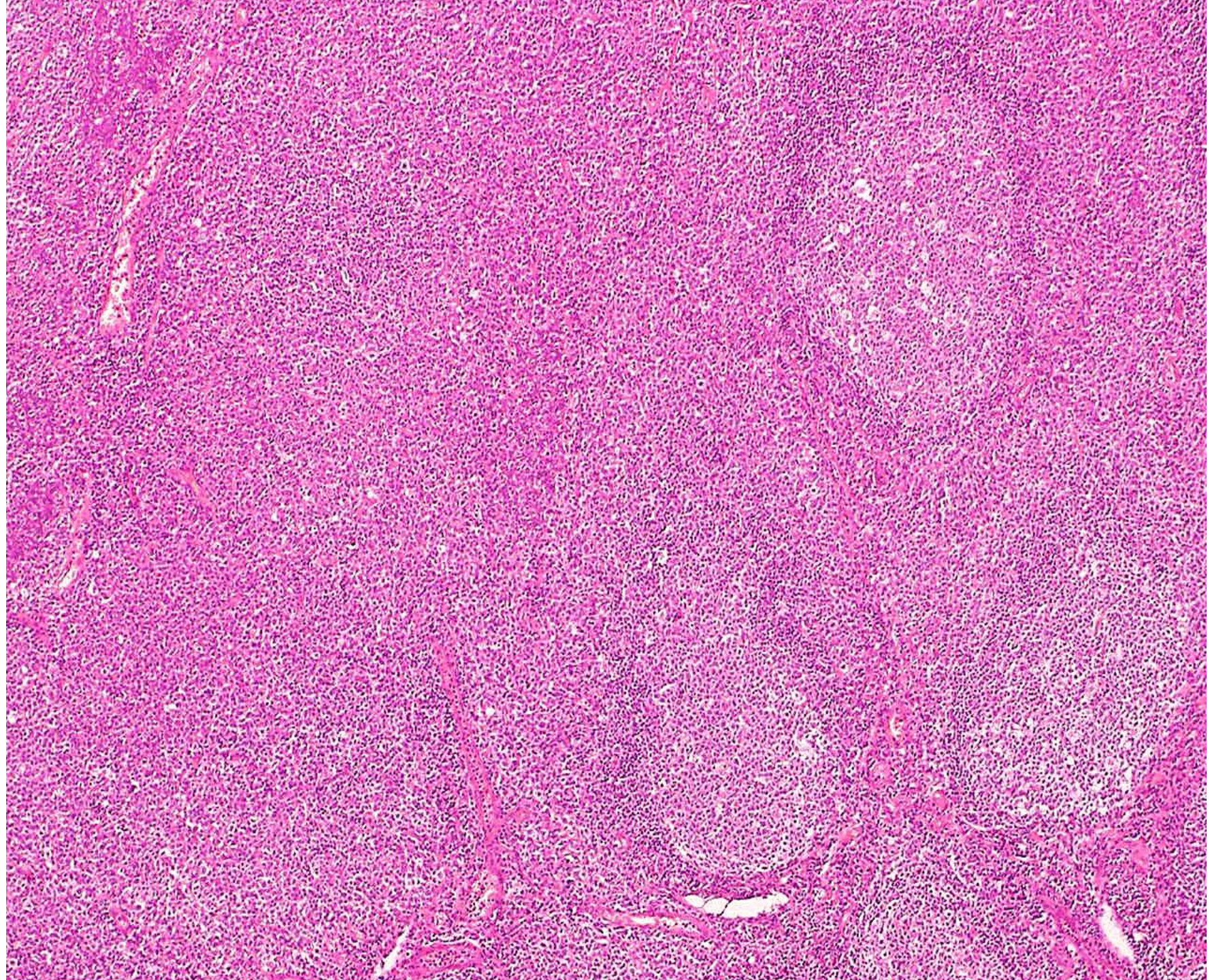
Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction

Ayoma D. Attygalle, Hongxiang Liu, Sima Shirali, Timothy C. Diss, Christoph Loddenkemper, Harald Stein, Ahmet Dogan, Ming-Qing Du, and Peter G. Isaacson

- 6 cases (4 tonsil, 2 appendix)

- Histopathology
  - Follicular hyperplasia
    - Some motheaten consistent with partial colonisation
  - Expanded marginal zone
  - B cells in epithelium
    - In tonsil – increased B cells in crypt epithelium
    - In appendix – focal invasion of crypt epithelium reminiscent of lymphoepithelial lesions

BLOOD 2004



IRTA1

- Surface B cell receptor that is related to the Fc receptor and cell adhesion molecule families
- In tonsil expression is confined to intra-epithelial and subepithelial B cells (Falini et al, BLOOD; 2003).
- Expressed in intra-epithelial B cells of acquired MALT
- In MALT lymphoma expression is restricted to cells forming lymphoepithelial lesions

- Expression is probably linked to epitheliotropism in B cells

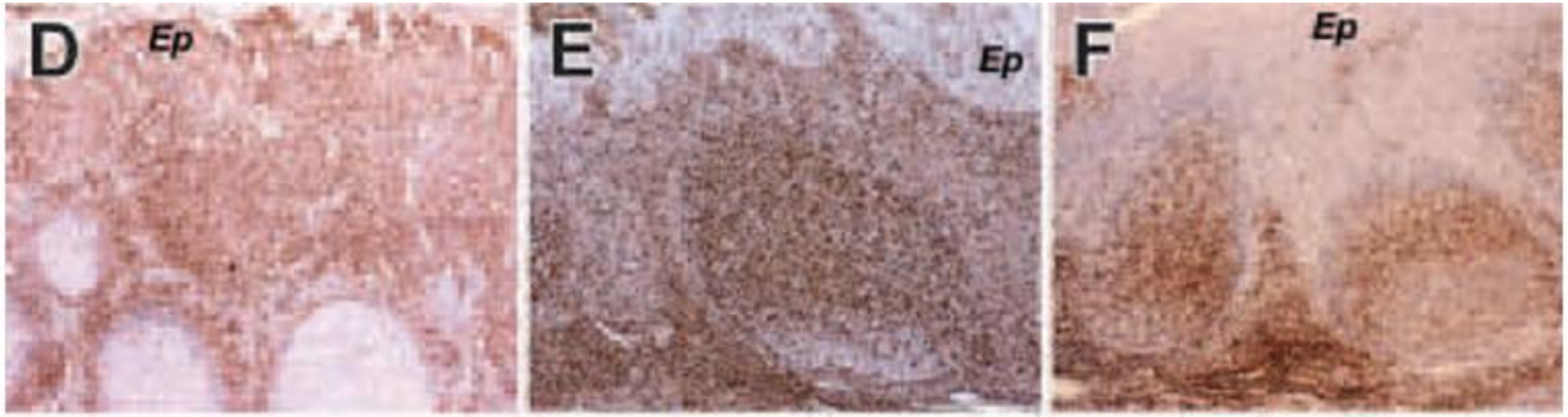
CD27 in subepithelial B cells

- Two populations have been described
  - High expression mutated
  - Low expression unmutated

- In atypical marginal zone hyperplasia
  - Intra-epithelial B cells are **unmutated B cells** (CD27-)

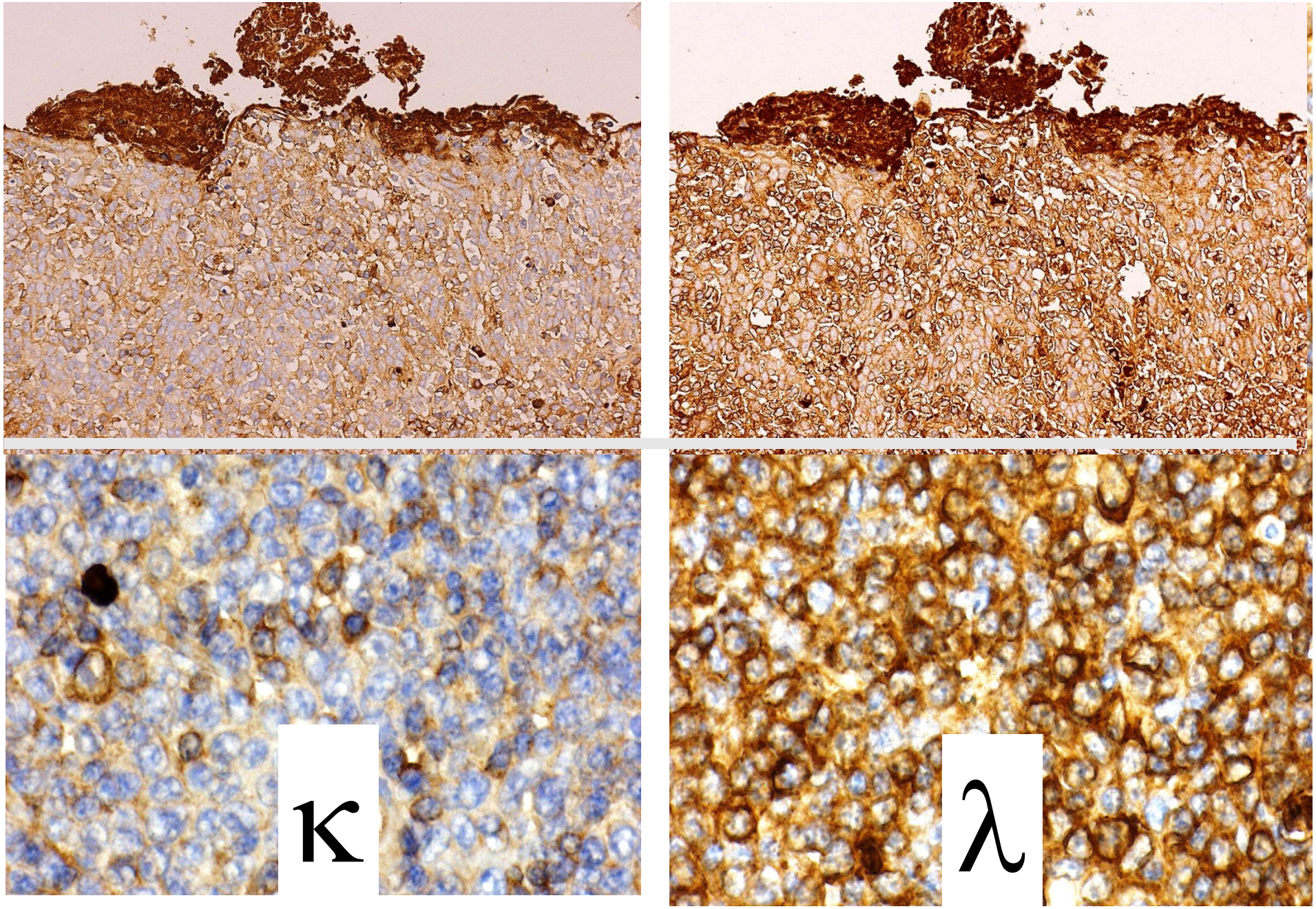
Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction

Ayoma D. Attygalle, Hongxiang Liu, Sima Shirali, Timothy C. Diss, Christoph Loddenkemper, Harald Stein, Ahmet Dogan, Ming-Qing Du, and Peter G. Isaacson



D IRTA1 +
E CD43 +
F CD27 -

BLOOD 2004


κ
λ

Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction

Ayoma D. Attygalle, Hongxiang Liu, Sima Shirali, Timothy C. Diss, Christoph Loddenkemper, Harald Stein, Ahmet Dogan, Ming-Qing Du, and Peter G. Isaacson

POSITIVE	NEGATIVE
CD20	CD27
IRTA1	CD10
CD43	MUM1
CD21	
IgM, IgD (weak)	
bcl-2	
Lambda light chain restriction	

BLOOD 2004

Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction

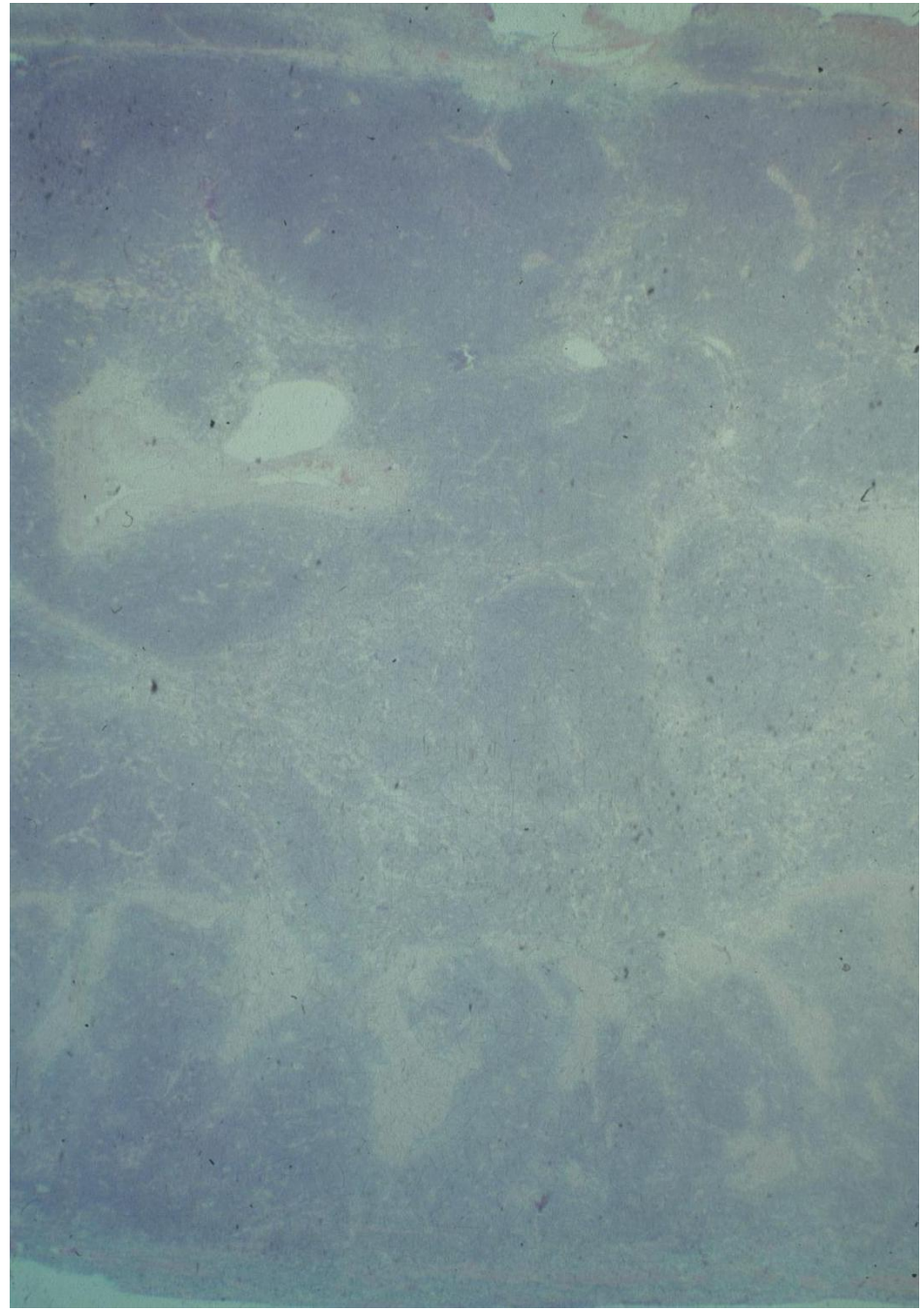
Ayoma D. Attygalle, Hongxiang Liu, Sima Shirali, Timothy C. Diss, Christoph Loddenkemper, Harald Stein, Ahmet Dogan, Ming-Qing Du, and Peter G. Isaacson

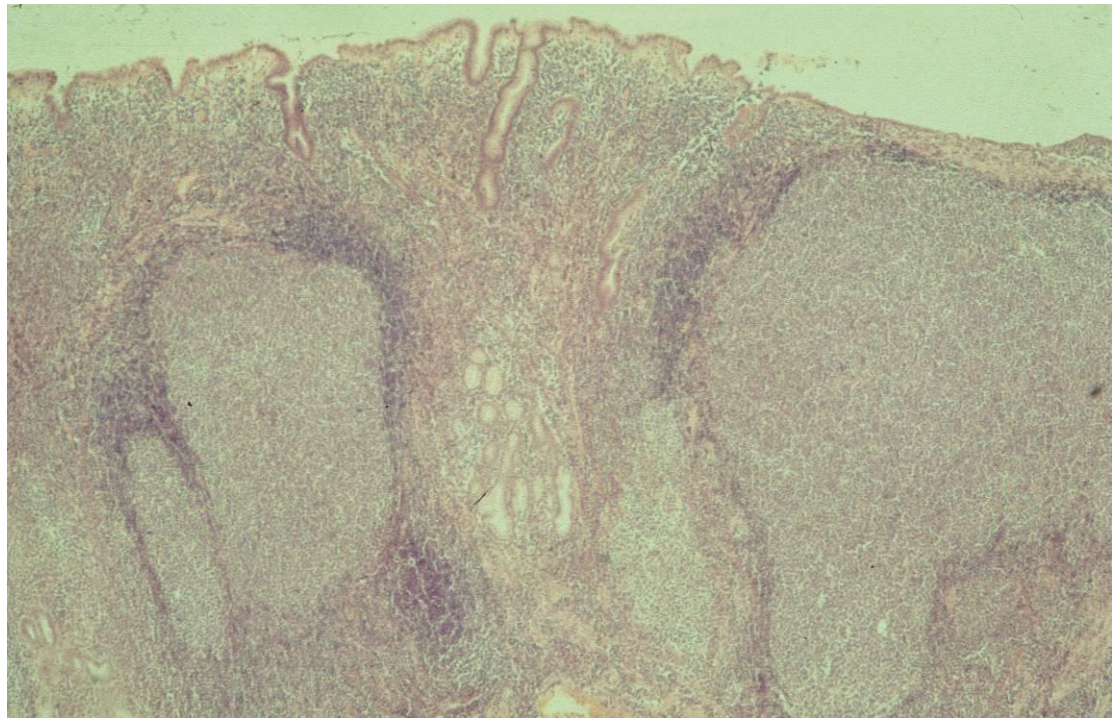
Blood 2004;104: 3343-3348

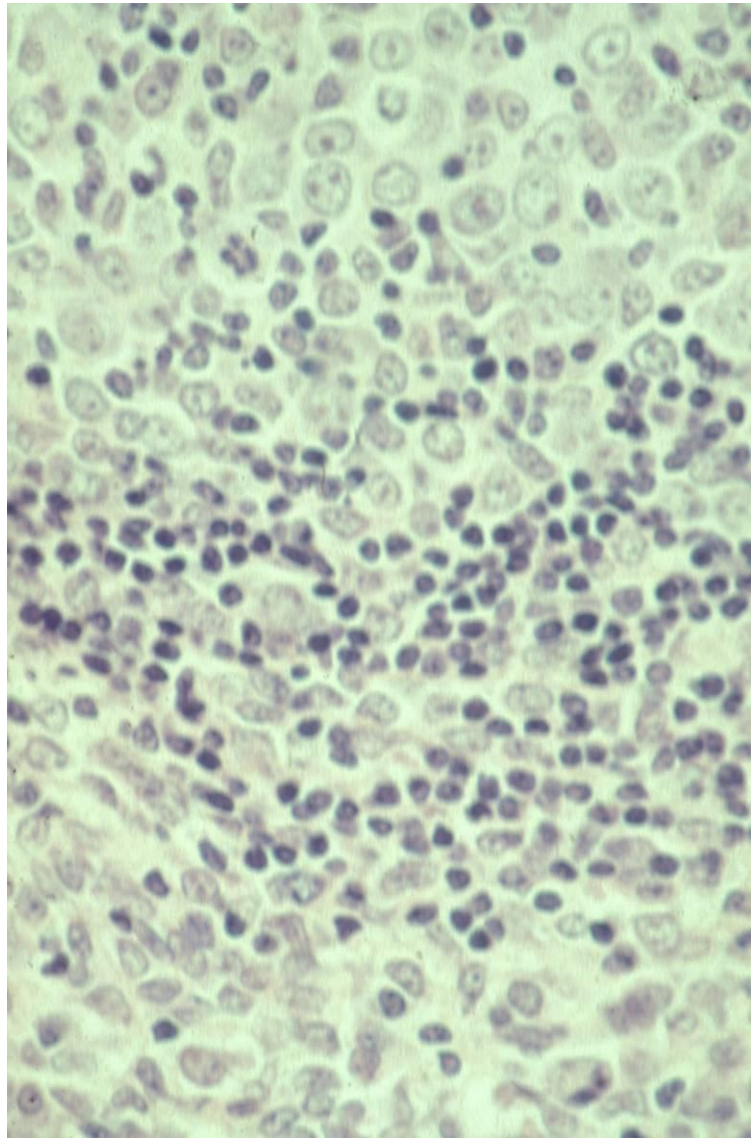
	Extranodal marginal zone hyperplasia	Extranodal marginal zone lymphoma
Site	Tonsil, appendix	Rare at sites of natural MALT
Age	Children	Adults, rare in children
IHC		
CD43	+	+/-
CD27	-	+
IgL	Lambda	Kappa or Lambda
Clonality	Polyclonal	Monoclonal

EXTRANODAL MARGINAL ZONE LYMPHOMA Differential Diagnosis

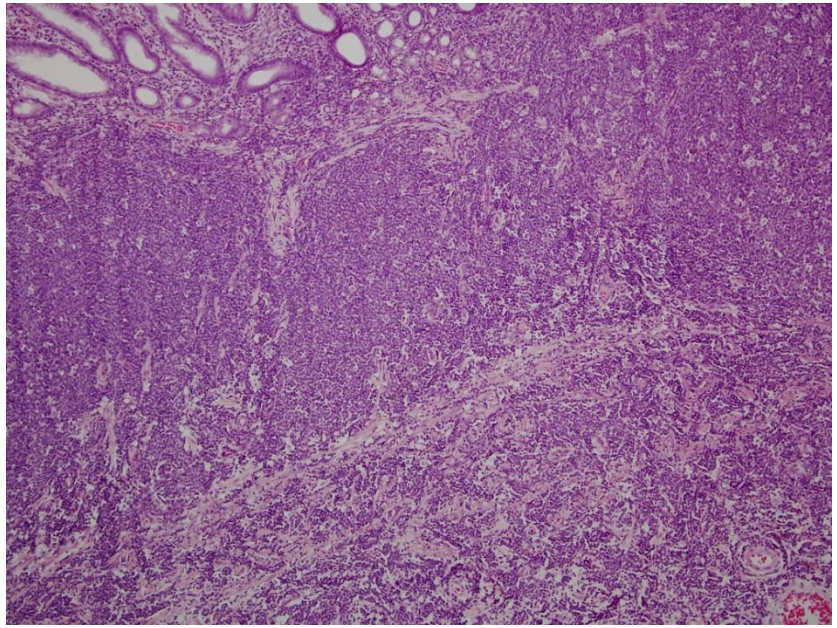
- Lymphoma vs Reactive
- Other low grade B cell lymphomas

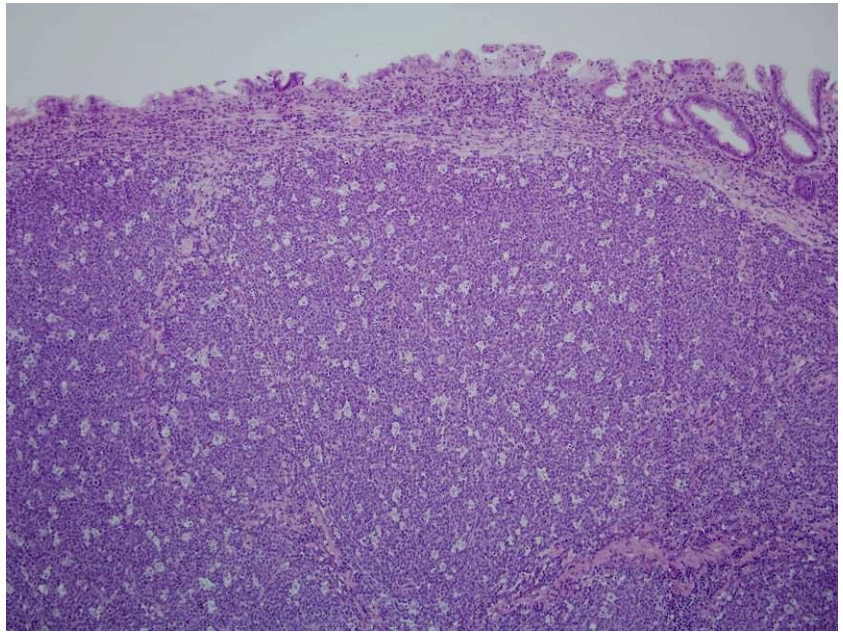


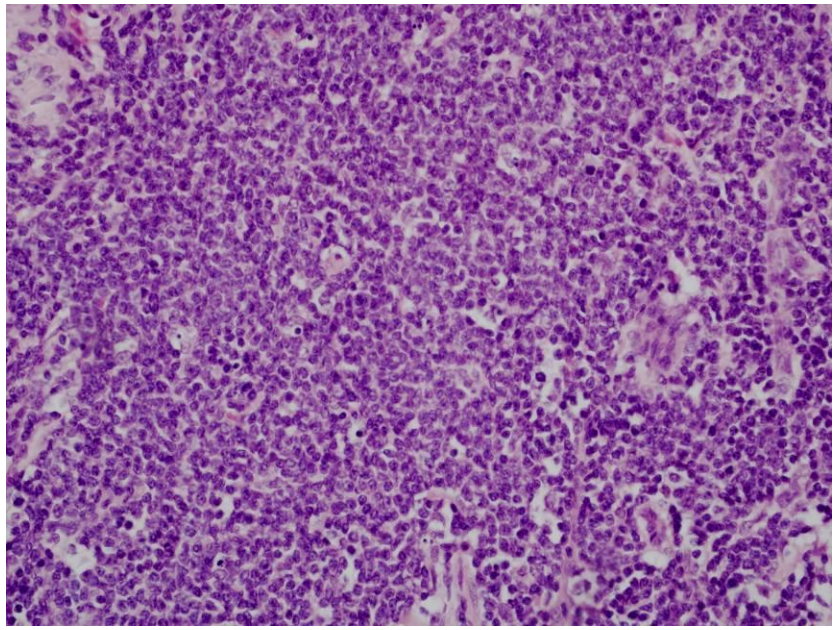


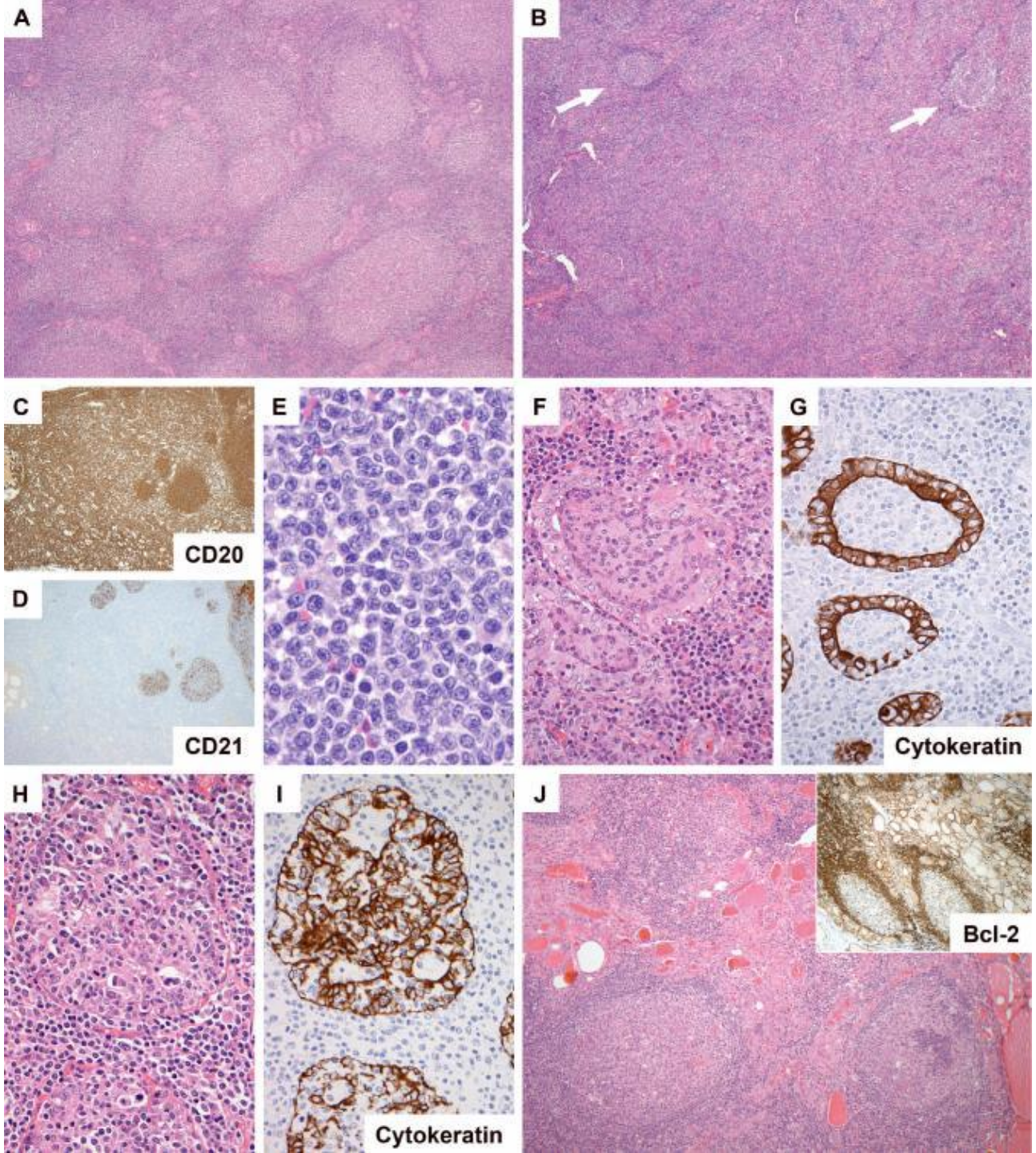


Follicular lymphoma









Follicular Lymphoma of the Thyroid Gland
Bacon CM et al
Am J Surg Pathol 2009; 33: 22-34

EXTRANODAL MARGINAL ZONE LYMPHOMA Differential Diagnosis

- Lymphoma vs Reactive
- Other low grade B cell lymphomas
- TFH lymphoma

Expansion of PD1-positive T Cells in Nodal Marginal Zone Lymphoma:

A Potential Diagnostic Pitfall

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Abstract

The diagnosis of nodal marginal zone lymphoma (NMZL) can be challenging, with the differential diagnosis including other low-grade B-cell lymphomas, reactive hyperplasia, and even some cases of peripheral T-cell lymphoma (PTCL). PTCL may have a perifollicular growth pattern mimicking NMZL. We and others have noted an atypical distribution of T-follicular helper (T_{FH}) cells in some cases of NMZL. This study was prompted by the diagnosis of NMZL in several cases in which a marked increase of T_{FH} cells, as determined by staining for programmed death-1 (PD1), had prompted suspicion for a diagnosis of PTCL. We analyzed PD1 staining in 48 cases of NMZL to characterize the extent and pattern of the PD1-positive infiltrate. Three main patterns of PD1 staining were identified: follicular pattern (peripheral, n= 16; central, n = 9; mixed, n = 3), diffuse pattern (n = 4), and a reduced or normal staining pattern in residual follicles (n = 16). A

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Histopathology 2019, **75**, 287–290. DOI: 10.1111/his.13858

Lesson of the month

Florid T follicular helper cell hyperplasia associated with extranodal marginal zone lymphoma: a diagnostic pitfall which may mimic T cell lymphoma

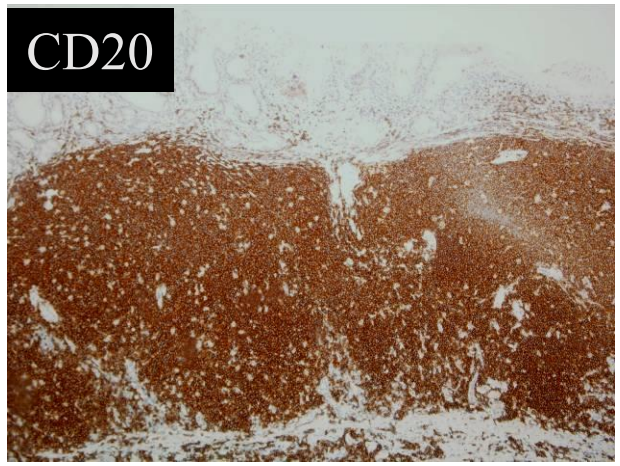
DOI: 10.1111/his.13858

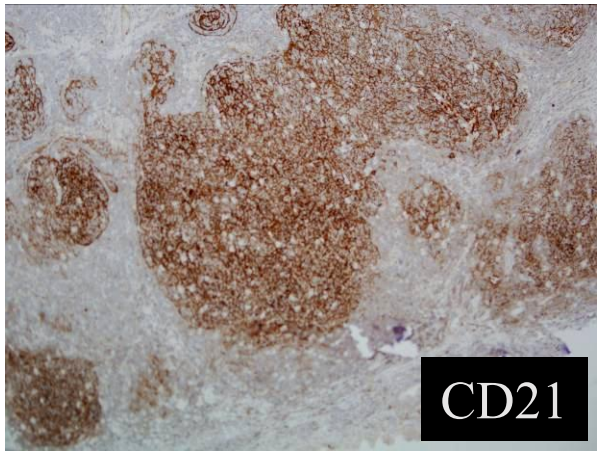
VROOBEL KM et al

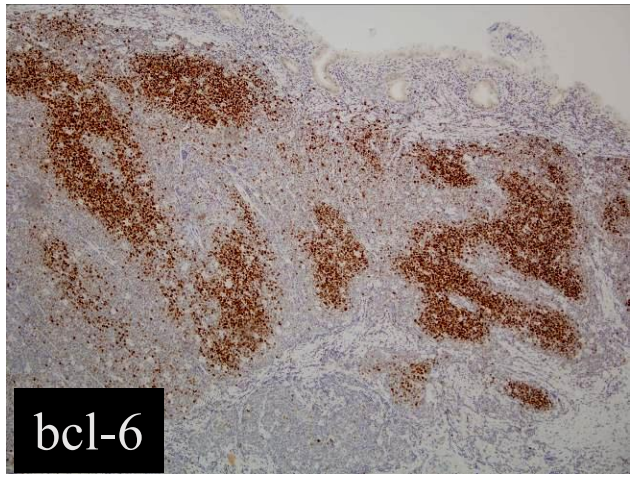
Follicular lymphoma

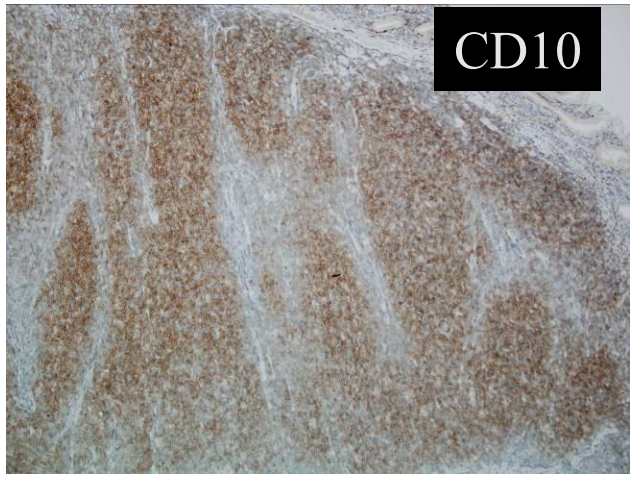
CD20 +
CD10 +
bcl-6 +
bcl-2 +/-

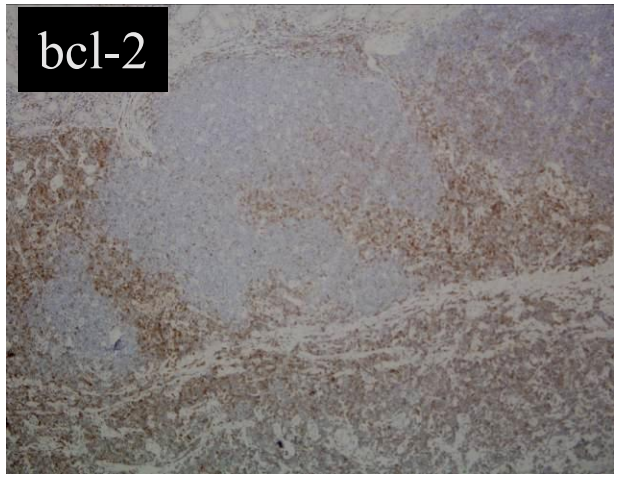
CD5 -
CD23 -
CyclinD1 -











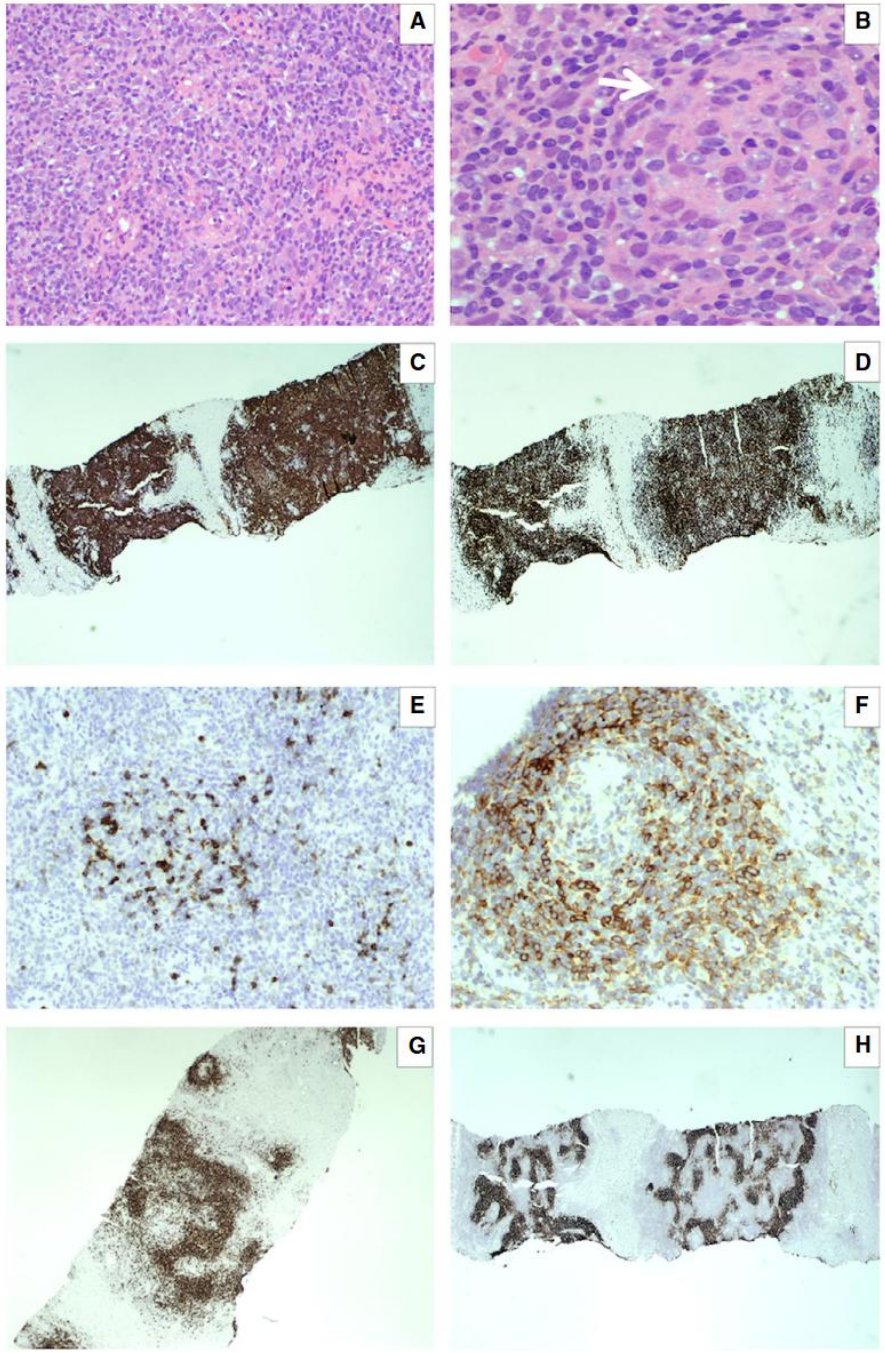
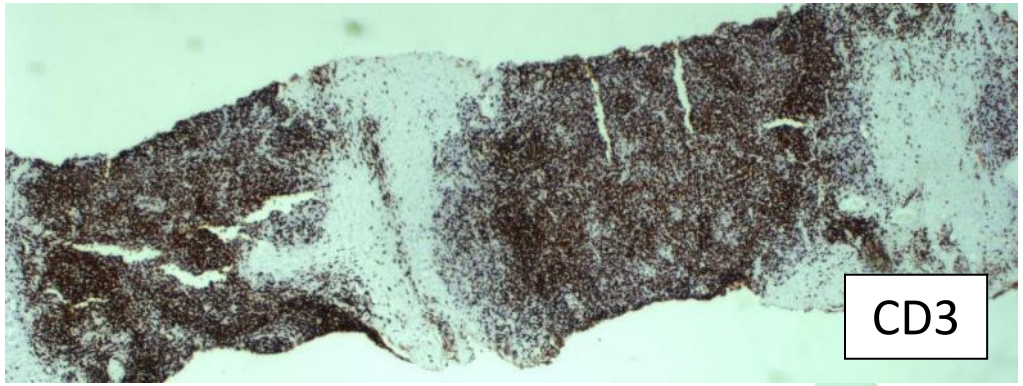
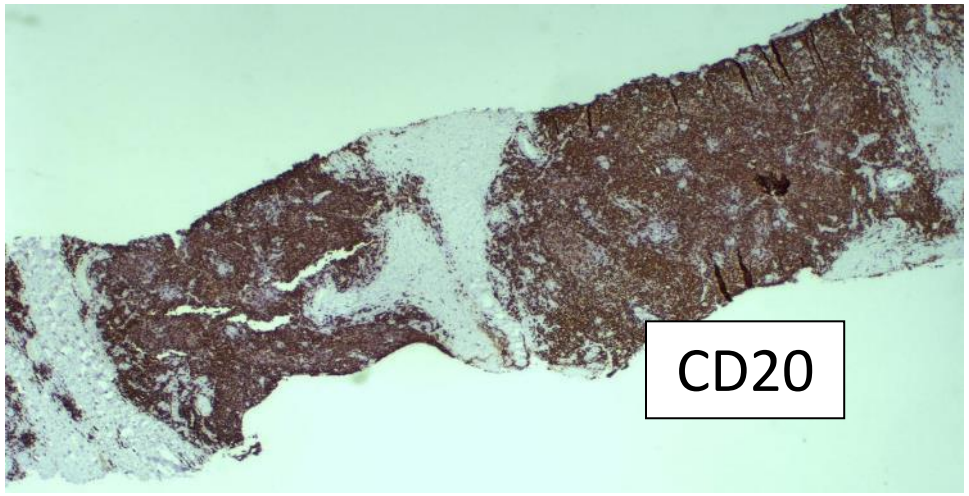
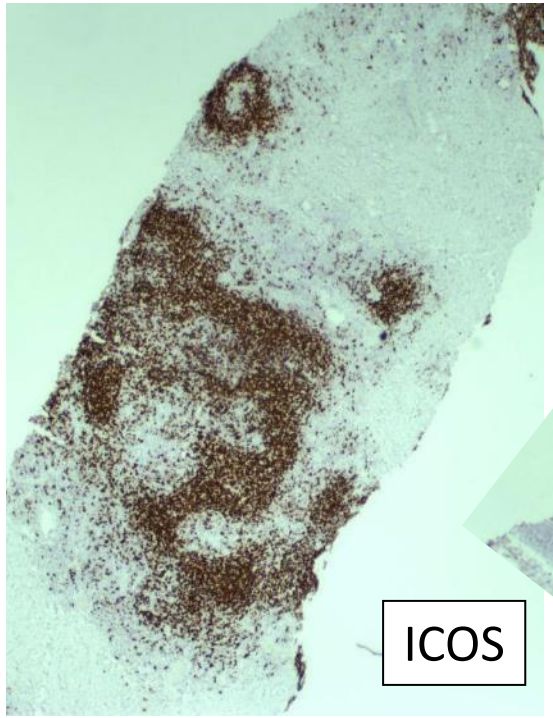


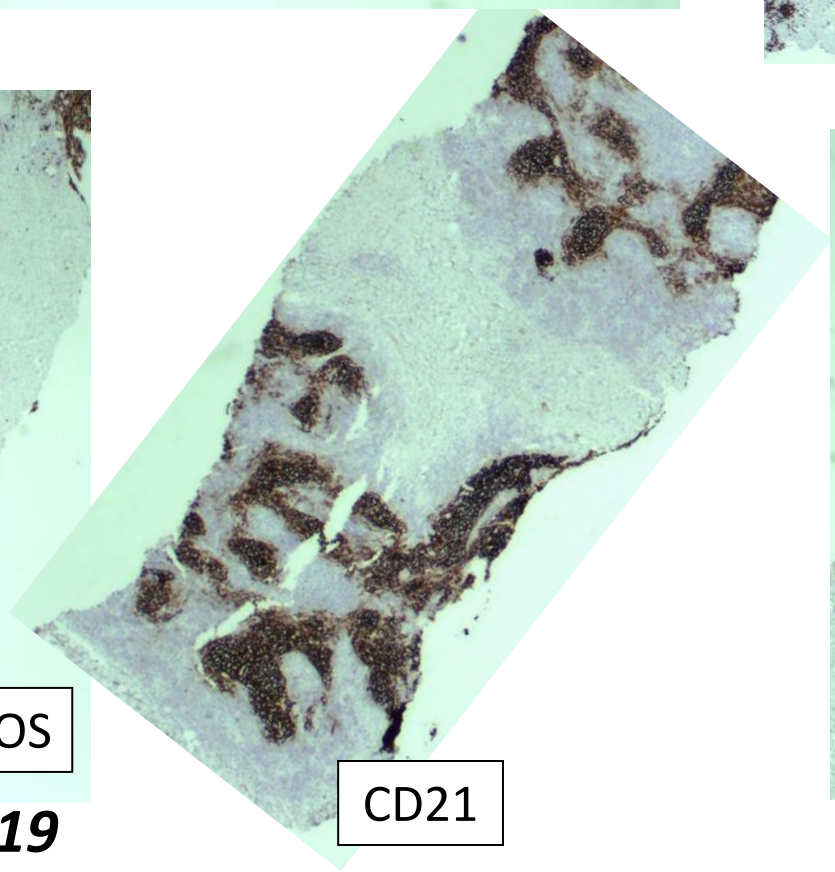
Figure 1. **A**, Haematoxylin and eosin (H&E). Polymorphous lymphoid infiltrate with some plasma cells and a degree of vascular proliferation. **B**, H&E. Polymorphous infiltrate with small regressed follicle (arrow). **C**, There was a dense CD20-positive small B cell population (×4) although there was a corresponding prominent CD3-positive T cell population (×4) **D**. T cells within the regressed follicle and spilling outside of it expressed CD10 (subset) (**E**), PD-1 (**F**) and ICOS (**G**). CD21 showed an expanded follicular dendritic cell meshwork (**H**), which was closely related to the ICOS-positive population.

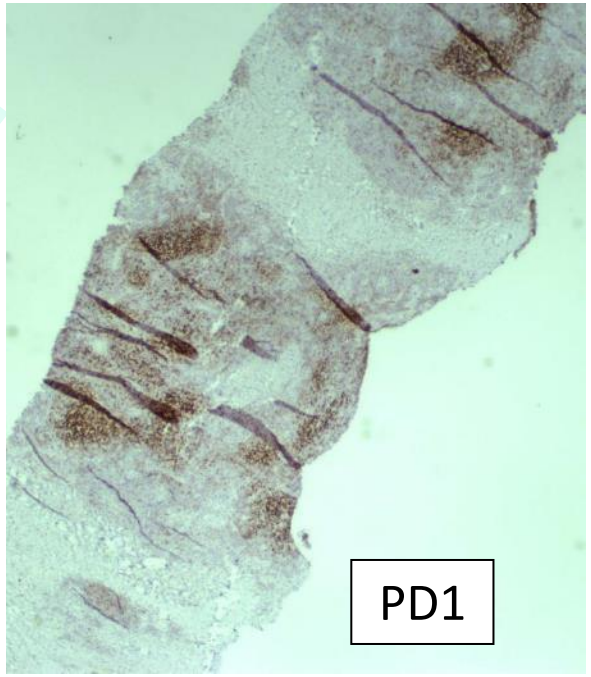
BEWARE!!! **Expansion of TFH cells in histologically low grade B-cell lymphomas**











62-year old female
Groin mass biopsy

Initial misdiagnosis: nTFHL-AI

Diagnosis: Extranodal marginal zone lymphoma of soft tissue

Vroobel et al 2019

Thank you