Marginal zone lymphoma: Associated autoimmunity & auto-immune disorders

Dr Andrew Wotherspoon
Histopathology department
Royal Marsden Hospital
London, UK

MZL: Associated autoimmunity & auto-immune disorders

AI disorders

- affect 5-9% of the world population
- >80 chronic illnesses

B-cell NHL

- 10th most common cancer world wide
- 3-4% of all malignancies

Both seem to share the loss of regulatory checkpoints in the normal B-cell proliferation

Epidemiological studies - Associations between SS, SLE, HT, AIHA, ITP and NHL/MZL

AID	Study – type/period			Statistical analysis	Association estimate (95% CI)		Risk factors
	Author	Type	Period	RR/ OR/ SIR/PR	NHL	MZL	
SS	Zintzaras 2005 [21]	Meta-analysis	1974-2005	SIR[2]	18.8 (9.5-37.3)	-	Antigen-driven chronic inflammation, adenopathy; long-term disease; enlargement of the parotid gland, palpable purpura, lymphopenia (CD4); presence of a monoclonal component, Low C4, disappearance of a previously positive RF, GC-like structures within the salivary glands, high serum β2 microglobulin, low level of serum immunoglobulin.
	Engels 2005[11]	Case-control	1998-2000	OR	4.9 (0.6-43)	-	
	Ekstrom 2008 [15]	Case-control[1]	1992-2005	OR	4.75 (1.79-12.6)	30.6 (12.3-76.1)	
	Anderson 2009 [9]	Case-control	1993-2002	OR	1.9 (1.5-2.3)	6.6 (4.6-9.53)	
	Goldin 2009 [8]	Case-control*	1958-2000-	OR	11.7 (5.7-24)	-	
	Solans-Laque2011 [13]	Cohort	1988-2008	SIR	15.6 (8.7-28.2)	-	
	Fallah 2014[12]	Cohort	1964-2010	SIR	4.9 (4.2-5.8)	-	
SLE	Zintzaras 2005 [21]	Meta-analysis	1974-2005	SIR[2]	7.4 (3.3-17)	-	Antigen-driven chronic inflammation, Leukopenia, chronic thrombocytopenia, hyperglobulinemia, positive serologies (anti-dsDNA, anti-SM, anti-phospholipid antibody); pulmonary infiltrates and/or recurrent pneumonia. Sicca symptoms; SLICC/ACR damage index reflecting high disease activity.
	Engels 2005 [11]	Case-control	1998-2000	OR	1.3 (0.3-5.6)	-	
	Ekstrom 2008 [15]	Case-control[1]	1992-2005	OR	2.69 (1.68-4.3)	7.52 (3.39-16.7)	
	Anderson 2009 [9]	Case-control	1993-2002	OR	1.5 (1.2-1.9)	2.8 (1.7-4.7)	
	Goldin 2009[8]	Case-control*	1958-2000-	OR	3.3 (2.1-5.3)	-	
	Bernatsky 2013 [18]	Case-cohort	1958-2009	SIR	4.4 (3.5-5.5)	-	
	Fallah 2014[12]	Cohort	1964-2010	SIR	4.4 (3.6-5.3)	-	
	Dasanu 2015[10]	Case-cohort	2008-2013	PR	-	0.04% (p=0.666)	
HT	Thieblemont 2002[39]	Cohort	1987-2000	PR	-	23%	Antigen-driven chronic inflammation, GC-like structures within the thyroid gland.
	Anderson 2009 [9]	Case-control	1993-2002	OR	1.1(0.8-1.4)	-	
	Goldin 2009 [8]	Case-control*	1958-2000-	OR	3.0 (1.2-7.5)	1.0 (0.4-2.2)	
	Fallah 2014	Cohort	1964-2010	SIR	1.4 (1.2-1.6)	-	
	Dasanu 2015[10]	Case-cohort	2008-2013	PR	-	20.8% (p=0.037)	
AIHA	Ekstrom 2008[15]	Case-control[1]	1992-2005	OR	2.57 (1.27-5.21)	2.23 (0.24-21.0)	Antigen-driven chronic inflammation.
	Anderson 2009 [9]	Case-control	1993-2002	OR	6.5 (4.4-9.4)	-	
	Goldin 2009[8]	Case-control*	1958-2000-	OR	5.0 (2.5-9.7)	-	
	Fallah 2014[12]	Cohort	1964-2010	SIR	27.2 (21.5-34)	-	
	Dasanu 2015[10]	Case-cohort	2008-2013	PR	-	0.04% (p<0.01)	
ITP	Ekstrom 2008[15]	Case-control[1]	1992-2005	OR	2.13 (0.47-9.73)	-	Antigen-driven chronic inflammation.
	Goldin 2009[8]	Case-control*	1958-2000-	OR	2.4 (1.0-5.5)	-	
	Fallah 2014[12]	Cohort	1964-2010	SIR	7.5 (5.9-9.4)	-	
	Dasanu 2015[10]	Case-cohort	2008-2013	PR	-	20.8% (p<0.01)	

AID: autoimmune disease; SS: Sjögren Syndrome; SLE: Systemic Lupus Erythematosus; HT: Hashimoto thyroiditis; AIHA: Autoimmune haemolytic anaemia; ITP: Idiopathic thrombocytopenic purpura; RR: relative risk; OR: odds ratio; SIR: Standardized incidence rate; PR: prevalence; NHL: non-Hodgkin lymphoma; MZL: marginal zone lymphoma; RF: rheumatoid factor; GC: germinal centre; SLICC/ACR: Systemic Lupus International Collaborating Clinics/ American College of Rheumatology

MZL: Associated autoimmunity & auto-immune disorders

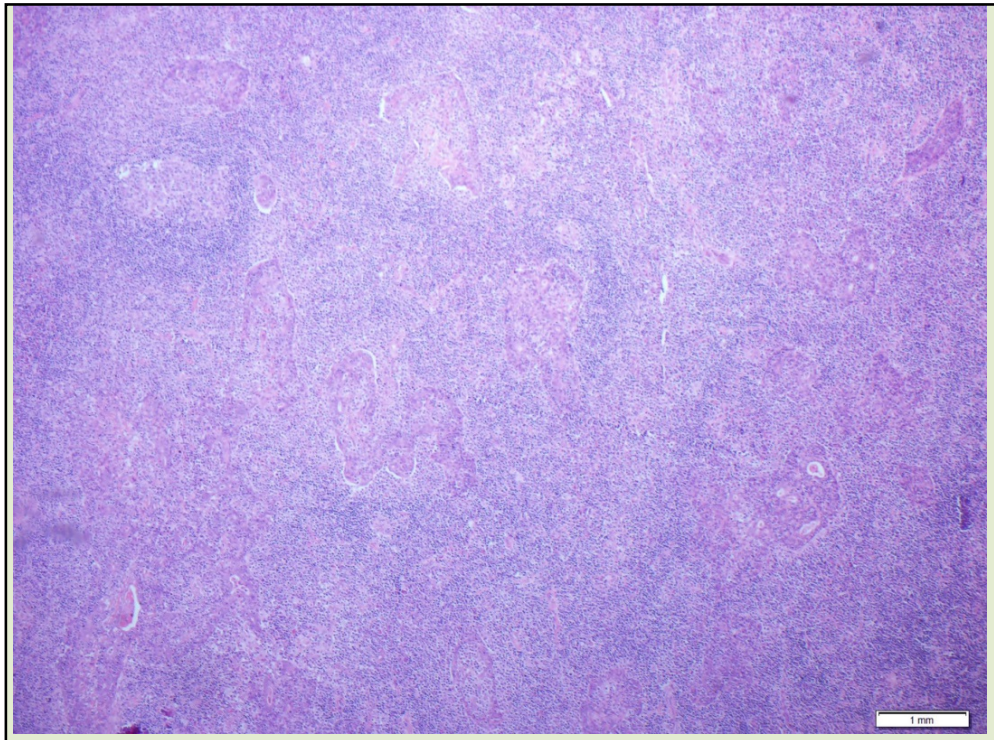
Lymphomagenesis in the context of autoimmunity

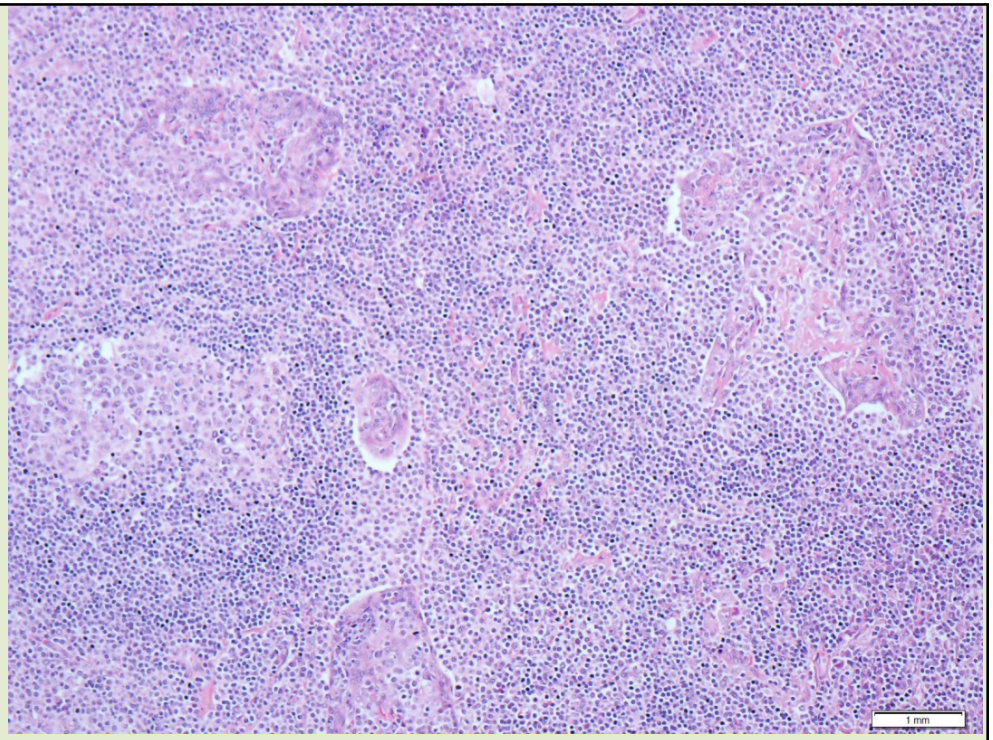
- Chronic inflammatory response & AG stimulation
- Immunosurveillance deficiency
- Resistance to apoptosis & deregulate lymphocyte reactivity
- Control of B-cell activation
  - NF-kB: regulates survival and proliferation in B cells;
  - BAFF (B-cell activating factor): Lower levels lead to immunodeficiency, higher levels to immunological hyperactivity/ autoimmunity;
- Immunosupressive treatment

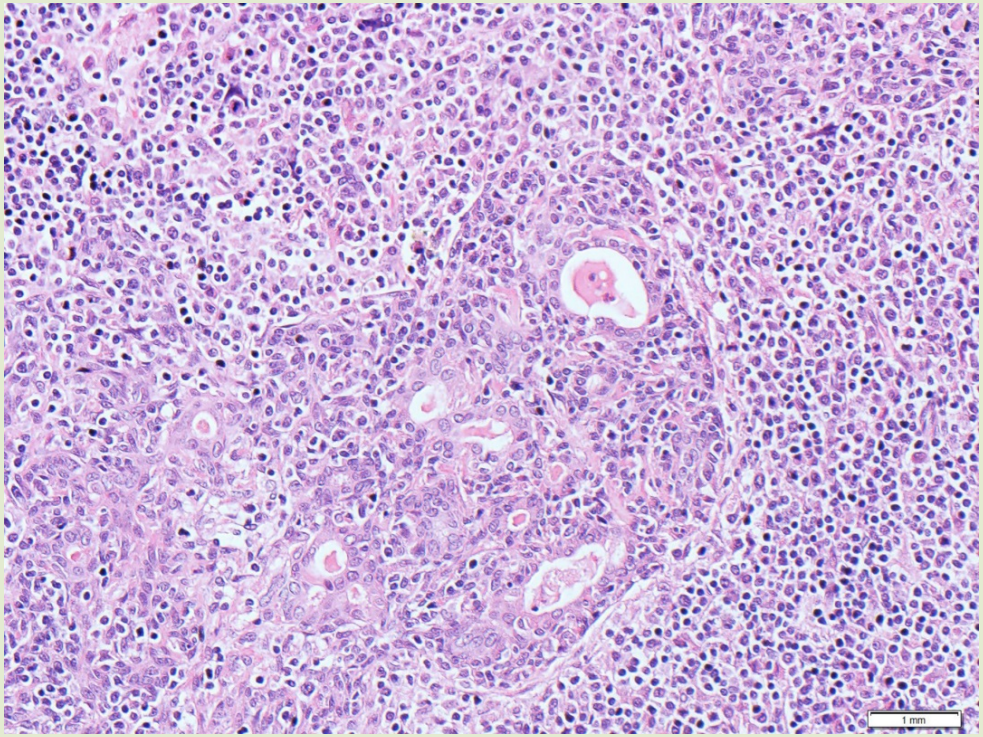
MZL: Associated autoimmunity & auto-immune disorders

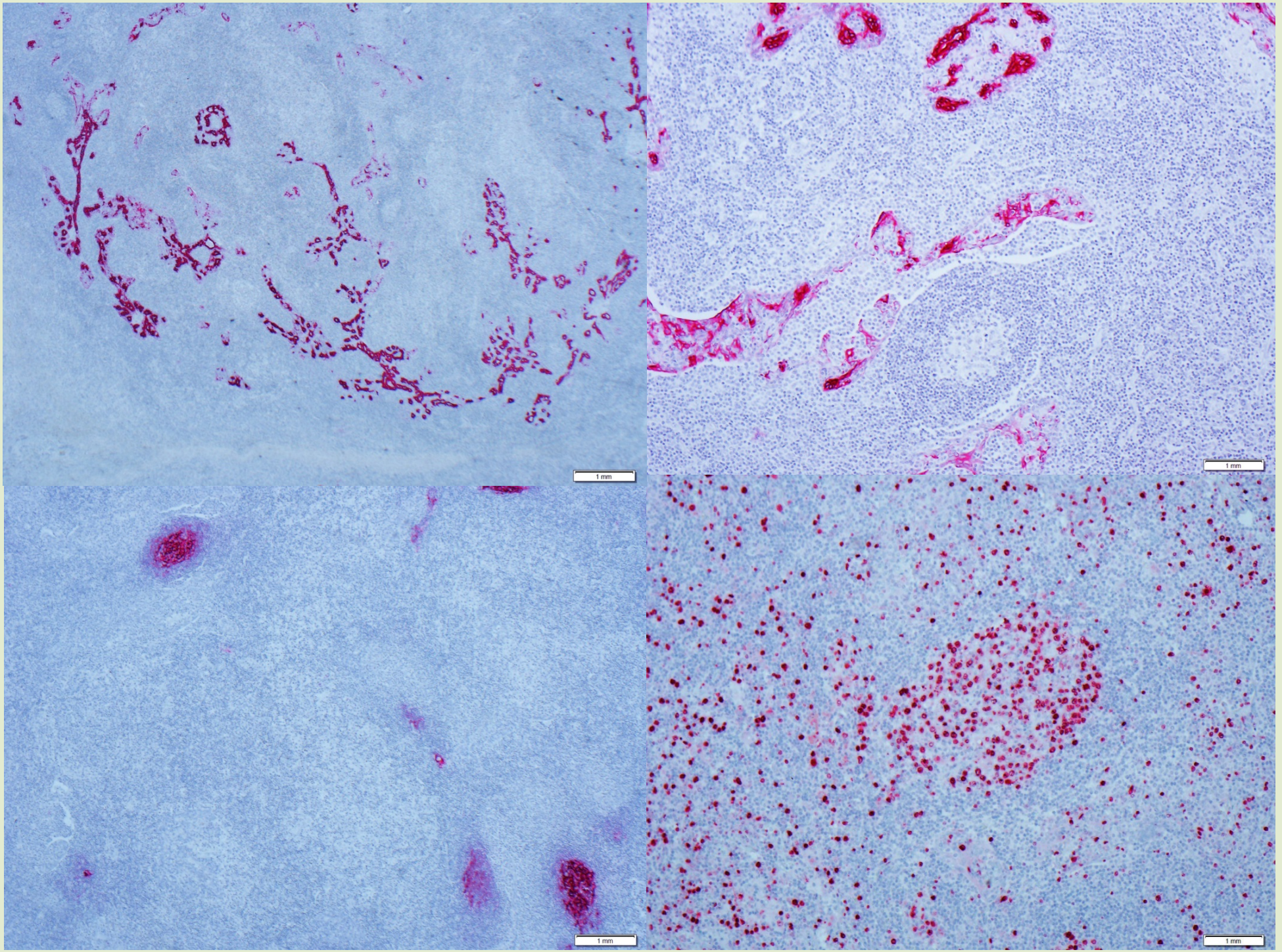
Sjögren Syndrome (SS)

- 3rd most common systemic AID
- 9F:1M
- Onset 40-60y
- Chronic inflammation of the exocrine glands
  - Acquired MALT
  - Epithelium destruction
- ↑RR6.6x to develop a lymphoma
- ↑RR30x to develop ENMZL of the salivary gland
- Average interval between dx (SS-ENMZL): 7.5y


1 mm


1 mm

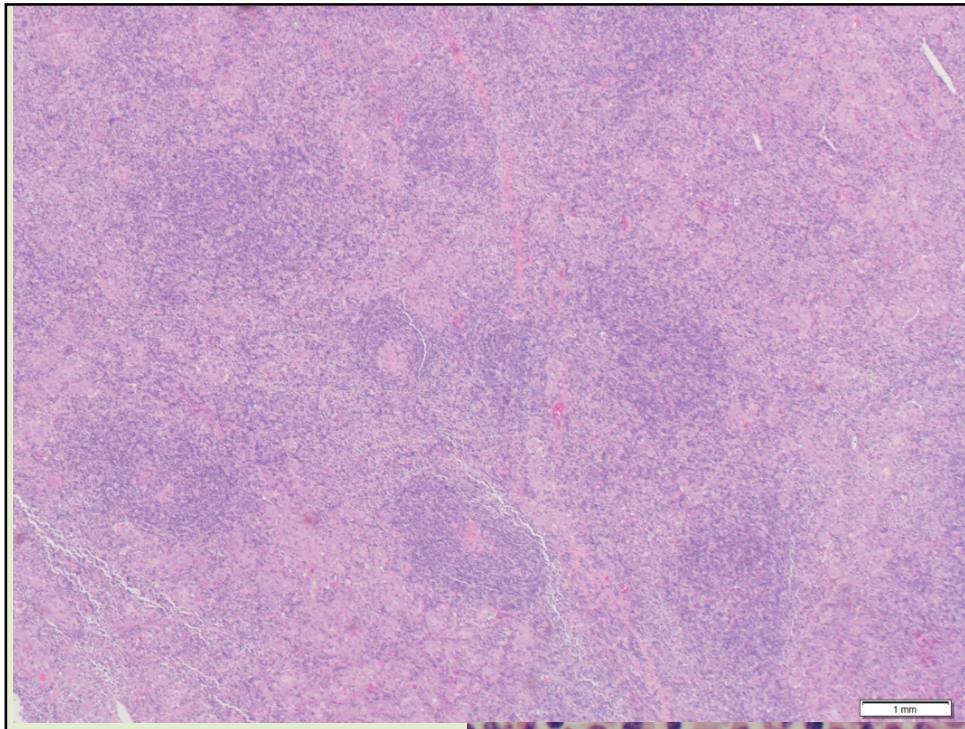

1 mm

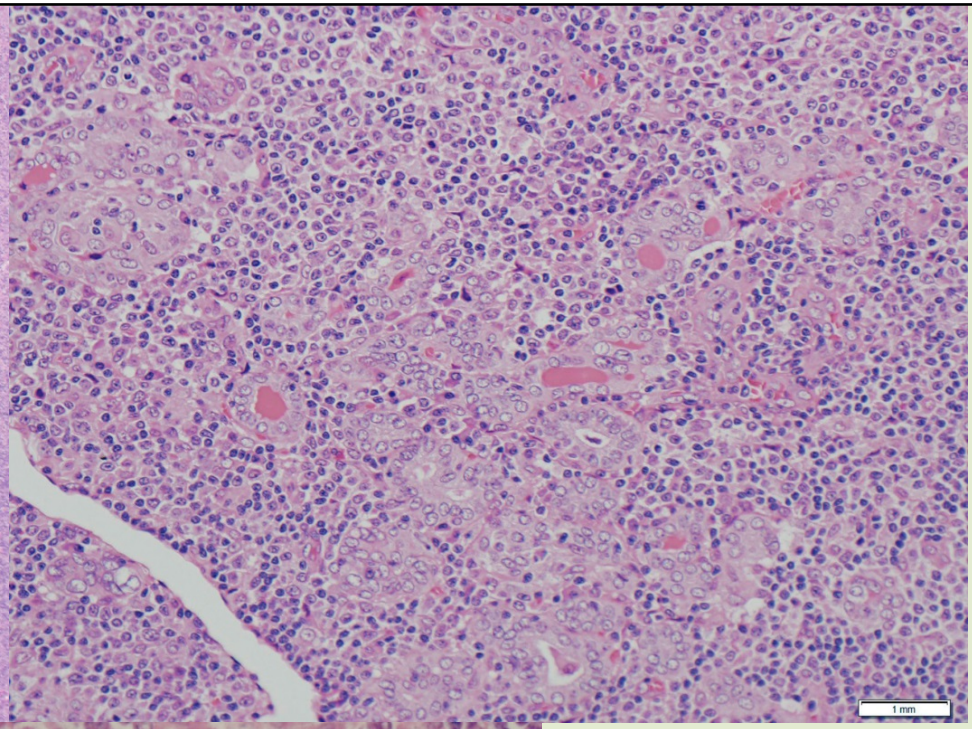

1 mm
1 mm
1 mm
1 mm

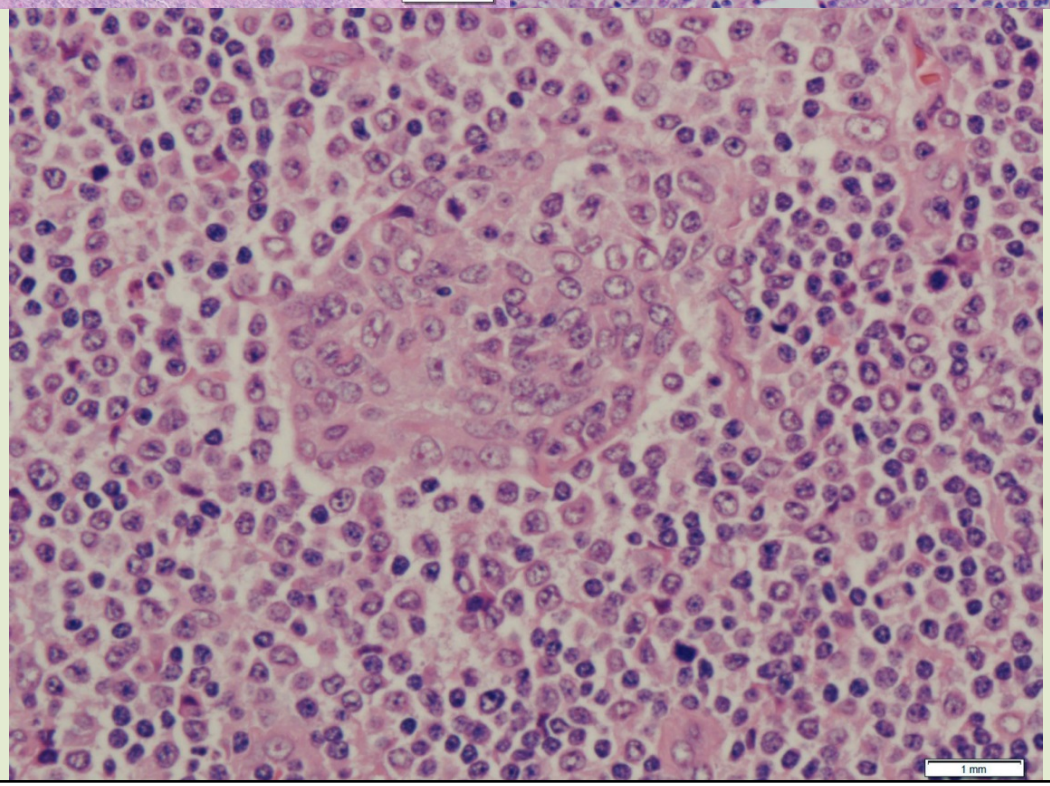
MZL: Associated autoimmunity & auto-immune disorders

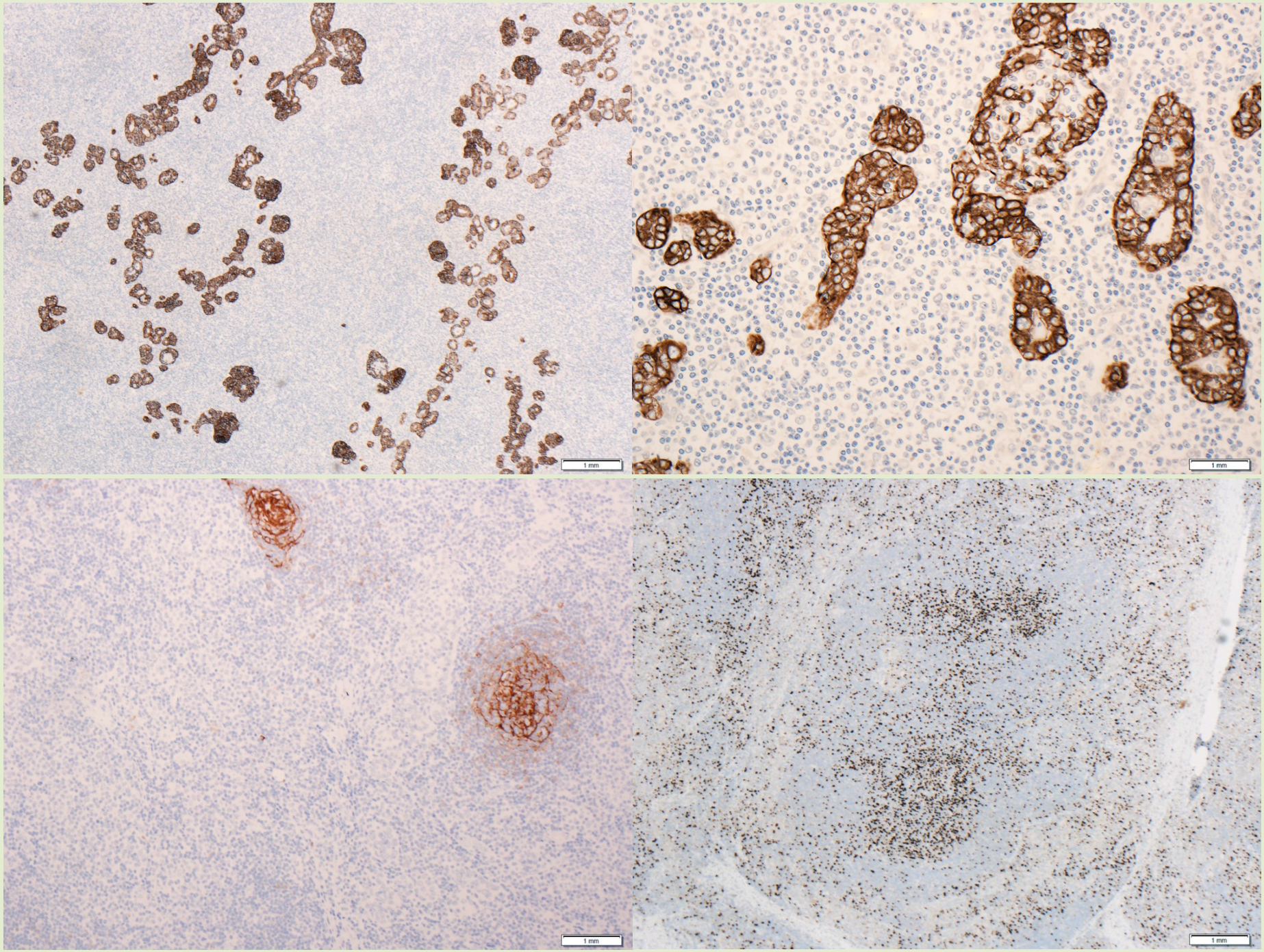
Hashimoto's Thyroiditis (HT)

- Affects mostly women
- Onset 45-65y
- Chronic inflammation
  - Acquired MALT
  - Atrophic thyroid follicles
  - Epithelium destruction
- ENMZL 25% of all primary thyroid lymphoma (PTL)
- HT → PTL: 40-80x greater risk than in general population
- HT→ENMZL: 67x risk
- HT-associated ENMZL is 3x more common in women (peak at 70y)
- Diagnostic interval HT→ENMZL: 2-3 decades
- HT patients are also at a greater risk of developing MALT lymphomas in organs other than the thyroid


1 mm


1 mm


1 mm


1 mm
1 mm
1 mm
1 mm

MZL: Associated autoimmunity & auto-immune disorders

Systemic lupus erythematosus (SLE)

- Systemic AIDs
- Affects mostly women
- Systemic chronic inflammation
- NHL risk is increased 2.7-4.1x
- Average age at NHL dx: 50y
- Diagnostic interval SLE→NHL: 6.7-17.8y
- 7.5RR to develop ENMZL (although DLBCL is the most common lymphoma subtype associated to SLE)
- Role of immunosuppressant agents as a risk factor for NHL/ENMZL development is controversial.

MZL: Associated autoimmunity & auto-immune disorders

Immune thrombocytopenic purpura (ITP) & Autoimmune haemolytic anaemia (AIHA)

- These are frequent complications seen in the course of many NHL and AID
    - Both are seen in about 10-15% of patients with SMZL and NMZL
- Overlapping occurrences: paraneoplastic syndrome?
    - More commonly occur synchronously with MZL diagnosis (Dasanu et al, 2015)
    - Other AIDs tend to precede MZL diagnosis

MZL: Associated autoimmunity & auto-immune disorders

Prognosis

- MZL: indolent behavior
- Most patients are diagnosed at an early stage (I/II)
- Management may include a 'watch & wait' approach
- ENMZL: OS>80% at 5y*
- NMZL: OS 55-75% at 5y*
- For non localised lymphomas, high tumour burden or high grade transformation: chemotherapy or chemo-immunotherapy

*Isaacson P. Extra nodal marginal zone lymphoma: MALT lymphoma. In: Harris N, Jaffe E, Vardiman J, Campo E, Arber D, editors. Hematopathology. 1st ed. Philadelphia, PA: Saunders Elsevier; 2011. p. 291e305.

*Isaacson PCA, Nakamura S, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Campo E, Swerdlow S, Harris N, et al., editors. WHO classification of tumors of the hematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC; 2008. p.214e7.

MZL: Associated autoimmunity & auto-immune disorders

Final comments

- The most consistent associations AID-ENMZL
  - SS
  - HT
  - SLE
  - ITP & AIHA
- Chronic antigenic stimulation plays a key role in most MZL
- AID are less frequently reported in SMZL and NMZL.
- AID-related risk factors for lymphoma development are thought to be :
  - Older age at dx;
  - Long standing disease;
  - Severity of disease;